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Therapeutic Review
Inhaled Corticosteroids

Overview/Summary

The inhaled corticosteroids (ICS) are a therapeutic class consisting of seven agents that are all Food and Drug Administration (FDA) approved for the maintenance treatment of asthma as prophylactic therapy. Some of the agents in this class also have the additional indication for use in asthma patients who require systemic corticosteroid therapy where the addition of an ICS could reduce or eliminate the need for the systemic corticosteroid. Currently none of the ICS agents are available as generic entities.[1-10]

These medications are also used for non-FDA approved indications, such as the treatment of chronic obstructive pulmonary disease (COPD). Beclomethasone and flunisolide have both been used to treat newborn bronchopulmonary dysplasia. Beclomethasone has additionally been used for the treatment of fentanyl induced cough, cystic fibrosis, and occupational asthma. Budesonide has been used to treat croup, cystic fibrosis, pulmonary sarcoidosis, and chronic respiratory disease in the perinatal period.[1-11]

These agents are effective in the treatment of asthma due to their wide range of inhibitory activities against multiple cell types (e.g. mast cells, eosinophils) and mediators (e.g. histamine, cytokines) which are involved in the asthmatic response. ICSs exert their anti-inflammatory effects by binding to the glucocorticoid receptors with a subsequent activation of genes involved in anti-inflammatory processes as well as an inhibition of pro-inflammatory genes involved in the asthmatic response. Inflammation is also a component of the COPD pathogenesis.[4,12]

Although ICS agents exert their effects through an identical mechanism of action, they differ in characteristics such as potency, dosing schedules, and dosage form availability. Clinical trials comparing ICS of differing potencies have shown that those of higher potencies do not demonstrate greater clinical efficacy than those of lower potencies when administered at equipotent doses.[13,14] Clinical trials have additionally failed to demonstrate any major differences in clinical efficacy between any of the available ICS agents.[14-16,23-61] The most common adverse events associated with the ICS as a class include oral candidiasis, cough at the time of inhalation, dysphonia, and headache.[15]

Current treatment guidelines published by the National, Heart, Lung, Blood Institute (NHLBI) indicate that the ICS agents are the most potent and consistently effective long-term controller medications for asthma patients of all ages. As such, these agents are recommended as first-line therapy for long-term control of persistent asthma symptoms in all age groups. The guidelines further state that although ICS agents do reduce both impairment and risk of asthma exacerbations, they do not appear to alter the progression or underlying severity of the disease. Of note, the NHLBI guidelines do not specifically recommend one ICS agent as possessing greater clinical efficacy or as a preferred agent over the other medications within the therapeutic class.[17]

The NHLBI guidelines also discuss the issue of growth velocity suppression in children treated with ICS agents. The guidelines indicate that the benefits of treatment with ICS outweigh the concerns for growth, and that untreated or poorly controlled asthma can also cause a decrease in a child's growth. This adverse effect on growth rate associated with this therapeutic class does appear to be dose dependant; however, this effect is not considered predictable. Furthermore, the effect on growth velocity appears to occur mainly in the first several months of treatment and is generally small and not progressive. However, because of the possibility of growth suppression, ICS doses in children should be titrated to as low a dose as needed to maintain good asthma control and children should be monitored for potential growth rate

changes.[17] Clinical evidence regarding the effects of ICS on growth velocity suggests that although there does appear to be a decrease in the growth velocity of children being treated with long-term ICS agents, these patients will ultimately reach their normal predicted height.[15]

The Global Initiative for Asthma (GINA) guidelines recommend that ICS are the most effective anti-inflammatory medications for the treatment of persistent asthma for patients of all ages. Additionally, the GINA guidelines indicate that although ICS agents differ in potency and bioavailability, there have been few studies that have been able to demonstrate this difference as being of any clinical significance. The GINA guidelines also do not recommend a preferred ICS agent.[18]

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines on COPD recommend that if an initial as needed short-acting bronchodilator is not effective for symptom relief, then the use of long-acting bronchodilator should be initiated, as these agents are central to COPD symptom management. ICS are recommended as add-on therapy to whichever agent was selected for initial COPD maintenance therapy in patients with severe stage-III COPD who are patients with an FEV_1 ≤50% predicted and repeated exacerbations. ICSs do not modify the long-term decline of FEV_1 but have been shown to reduce the frequency of exacerbations, causing an overall improvement in health status.[19]

The National Institute for Clinical Excellence (NICE) COPD guidelines also recommend the use of ICSs as adjunctive agents to long-acting bronchodilators to decrease exacerbation frequency in patients with an FEV_1 ≤50% predicted and repeated exacerbations.[20]

As of as a result of the Clean Air Act and the Montreal Protocol on Substances that Deplete the Ozone Layer, the FDA made the decision to end production, marketing, and sale of all meter dose inhalers (MDIs) containing chlorofluorocarbons (CFCs) as their propellant by December 31, 2008. Currently, all CFC MDIs are being replaced by MDIs that utilize hydrofluoroalkane (HFAs) as their propellants. HFA inhalers provide the same level of safety and efficacy as CFC inhalers, but without causing damage to the ozone layer.[11,21,22] Currently, the only CFC-propellant ICS agents available include flunisolide (Aerobid®, Aerobid-M®), and triamcinolone (Azmacort®). An HFA formulated flunisolide inhaler will be released in the United States by the end of fourth quarter, 2009 under the brand name Aerospan™. Information as to when an HFA compliant triamcinolone formulation will be released was not available at the time of this review.[5,6,10, 11]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Beclomethasone dipropionate (QVAR®)	Inhaled corticosteroid	-
Budesonide (Pulmicort Flexhaler™, Pulmicort Respules®)	Inhaled corticosteroid	-
Ciclesonide (Alvesco®)	Inhaled corticosteroid	-
Flunisolide (Aerobid®§, Aerobid-M®§, Aerospan™)	Inhaled corticosteroid	-
Fluticasone propionate (Flovent Diskus®, Flovent HFA®)	Inhaled corticosteroid	-
Mometasone furoate (Asmanex Twisthaler®)	Inhaled corticosteroid	-
Triamcinolone acetonide (Azmacort®)§	Inhaled corticosteroid	-

HFA=hydroflouroalkane
* Aerospan™ is scheduled for release by fourth quarter, 2009.
§ CFC=chlorofluorocarbon.

Indications

Table 2. Food and Drug Administration Approved Indications[1-10]

Indication	Maintenance Treatment of Asthma as Prophylactic Therapy in Patients 12 Months to 8 Years of Age	Maintenance Treatment of Asthma as Prophylactic Therapy in Patients 4 Years of Age and Older	Maintenance Treatment of Asthma as Prophylactic Therapy in Patients 5 Years of Age and Older	Maintenance Treatment of Asthma as Prophylactic Therapy in Patients 6 Years of Age and Older	Maintenance Treatment of Asthma as Prophylactic Therapy in Patients 12 Years of Age and Older	Maintenance Treatment of Asthma as Prophylactic Therapy (Age Not Specified)	Asthma Patients Requiring Systemic Corticosteroid Therapy, Where the Addition of an Inhaled Corticosteroid May Reduce or Eliminate the Need for the Systemic Corticosteroid
Beclomethasone (QVAR®)			✔				✔
Budesonide (Pulmicort Flexhaler™)				✔			✔
Budesonide (Pulmicort Respules®)	✔						
Ciclesonide (Alvesco®)					✔		
Flunisolide (Aerobid®) (Aerobid-M®)						✔	✔
Flunisolide (Aerospan™)				✔			✔
Fluticasone (Flovent Diskus®) (Flovent HFA®)		✔					✔
Mometasone (Asmanex Twisthaler®)		✔					
Triamcinolone (Azmacort®)						✔	✔

HFA= hydrofluoroalkane.

Pharmacokinetics

Table 3. Pharmacokinetics[1-11]

Generic Name	Onset (hours)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Beclomethasone	0.5	<10	Yes	2.8
Budesonide	1-2	60	Yes	2-3
Ciclesonide	Not reported	≤20	Yes	6-7
Flunisolide	0.90-0.17	<1	Yes	1.8
Fluticasone	1	5	Yes	3.1
Mometasone	1.0-2.5	8	No	5
Triamcinolone	1.5-2.0	40	Yes	1.5

Clinical Trials

Numerous placebo controlled studies have demonstrated the efficacy of inhaled corticosteroid agents in the treatment of asthma, and these agents are considered the most effective agents in the long-term management of the disease. Head-to-head studies examining these agents however have been inconclusive in showing efficacy superiority of one specific agent over any other, regardless of the potency or dosage form of the inhaled corticosteroid agent used.[23-69]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Asthma				
Agertoft et al[23] Budesonide vs control group Patients were enrolled in a 1 to 2 year run-in period where their asthma medication was adjusted according to Danish guidelines. Those patients considered acceptably controlled without continuous ICS use, were then asked to change treatment to budesonide. The mean duration of budesonide treatment and mean daily budesonide dose at the time of adult height attainment was 9.2 years and 412 µg respectively.	PRO Children with asthma	N=332 10 years	Primary: Measured adult height in relation to the target adult height Secondary: Difference between measured height and target adult height in relation to(mean cumulative budesonide dose, duration of treatment, patient gender, age at beginning of budesonide treatment, age at which adult height was obtained, duration of asthma before budesonide start), growth rate of budesonide treatment compared to the run-in period	Primary: The measured and target adult height in the two groups was (173.2 cm, 172.9 cm) and (173.9 cm, 174.1 cm) for the budesonide and control group respectively. The mean differences between the measured and target adult heights were +0.3 cm (95% CI, -0.6 to 1.2) for the budesonide group, and -0.2 cm (95% CI, -2.4 to 2.1) for the control group. Secondary: Twenty children in the budesonide group did not achieve their adult height. Their mean cumulative dose of 1.25 g was not significantly different from that of children who had attained their adult height, which was 1.35 g (*P*=0.72). There was no significant correlation between the duration of treatment and the differences between the measured and target adult heights (*P*=0.16). The difference between measured and target adult heights was not significantly associated with the patient's gender (*P*=0.30), age at the beginning of budesonide treatment (*P*=0.13), age at which adult height was attained (*P*=0.82), or duration of asthma before the start of budesonide treatment (*P*=0.37). Budesonide was associated with a significant change in growth rate during the first years of treatment as compared with the run-in period. The mean growth rate was 6.1 cm/year (95% CI, 5.7 to 6.5) during the run-in period, 5.1 cm/year (95% CI, 4.7 to 5.5; *P*<0.001) during the first year of treatment, 5.5 cm/year (95% CI, 5.1 to 5.9; *P*=0.02) during the second year of treatment, and 5.9 cm/year (95% CI, 5.5 to 6.3; *P*=0.53) during the third year. Changes in growth rate during this period were not correlated with the differences between measured and target adult heights (*P*=0.44). The initial growth retardation was significantly correlated with age, with a more pronounce reduction in younger children (*P*=0.04). Children with a low standard deviation score for height before budesonide treatment had a smaller adult height than expected (*P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Baker et al[31] Budesonide 0.25 mg twice daily via nebulizer vs budesonide 0.5 mg twice daily via nebulizer vs budesonide 1 mg in the morning and placebo in the evening via nebulizer vs placebo twice daily	DB, MC, PC, PG, RCT Children, ages 6 months to 8 years, with a diagnosis of asthma as defined by accepted criteria	N=480 12 weeks	Primary: Changes in asthma symptom improvement score from baseline, PEF, improvements in FEV_1 Secondary: Not reported	Primary: Symptom scores within 2 weeks after starting treatment showed separation between active treatment groups and placebo. When symptom scores for all active treatment groups were combined, a statistically significant difference between active treatment compared with placebo was seen as early as day 2 for nighttime asthma symptoms, and day 5 for daytime asthma symptoms (P<0.05). There were statistically significant improvements in morning PEF in the 0.25 mg twice daily (10.9 L/min), 0.5 mg twice daily (24.8 L/min), and 1.0 mg once daily (17.1 L/min) treatment groups compared with placebo (P<0.030) and in evening PEF for each active treatment (16.8 L/min for 0.25 mg once daily; P<0.05, 19.2 L/min for 0.25 mg twice daily; P<0.05, and 21.0 L/min for 0.5 mg twice daily; P<0.010) except 1.0 mg once daily (14.1 L/min; P value not reported). All treatment groups showed numerical improvement in FEV_1 but the only improvement that was statistically significant for FEV_1 compared with placebo was for the 0.5 mg twice daily group (0.04 L/min vs 0.17 L/min; P=0.031). Secondary: Not reported
Rowe et al[25] Budesonide 1,600 µg/day via DPI vs placebo	DB, PC, RCT Patients aged 16 to 60 years presenting to the emergency department with acute asthma who were discharged with a nontapering course of oral prednisone (50 mg/day) for 7 days	N=1,006 21 days	Primary: Rates of relapse Secondary: QOL, rescue inhaler use, changes in pulmonary function, symptoms, global assessment, adverse effects, compliance	Primary: The budesonide group experienced fewer relapses (12 patients [12.8%]; 95% CI, 7 to 21%) than the placebo group (23 patients [24.5%]; 95% CI, 16 to 34%) by 21 days (P=0.049). This represents a 48% relapse reduction and suggests as few as 9 patients would require treatment with budesonide to prevent 1 relapse. Secondary: QOL scores were higher in the budesonide than that for the placebo group (P=0.001). The budesonide patients were using fewer mean albuterol inhalations in 24 hours compared with placebo patients (2.4 vs 4.2; P=0.01) at 21 days.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Mean and percent predicted peak flow and spirometry findings revealed no differences between the groups. At the conclusion of the study, the budesonide group had fewer symptoms of cough (*P*=0.004), breathlessness (*P*=0.001), wheezing (*P*=0.001), and nighttime awakenings (*P*=0.001) compared with placebo. Patients in the budesonide group assessed their asthma as more improved than those in the placebo group at 21-day follow-up (6.2 vs 5.2; *P*=0.001). Adverse effects were greater in the placebo group for both hoarseness and sore throat (*P*=0.02). The overall incidence of adverse effects associated with ICS use (insomnia, fluid retention, acne) was equal between the two groups. Self-reported compliance with the use of oral prednisone was high within the first week of care in both groups (94% for budesonide vs 96% for placebo; *P*=0.73). Self-reported compliance with budesonide was similar between the groups at 7 (100% for both groups) and 21 days (92% for budesonide vs 93% for placebo; *P*=0.95).
Sheffer et al[26] Budesonide (200 µg in children <11 years; 400 µg for those >11 years) once daily for 3 years via DPI vs placebo once daily for 3 years in addition to their usual asthma therapy	DB, PC, RCT: first 3 years OL: following 2 years Patients aged 5 to 66 years with mild persistent asthma for fewer than 2 years and no previous regular corticosteroid treatment	N=7,241 5 years	Primary: Time to the first severe asthma-related event; change in post-bronchodilator FEV_1 percent predicted from baseline to the end of the 5-year study period Secondary: Number of asthma-related events during the double-blind period; time to first addition of a steroid treatment	Primary: Budesonide reduced the risk of a first severe asthma-related event in patients with mild persistent asthma by 44% (HR, 0.56; 95% CI, 0.45 to 0.71; *P*<0.001). A significant improvement in both prebronchodilator and postbronchodilator FEV_1 percent values was observed after year 1 and year 3 of the study for the budesonide treatment group compared with the placebo arm. After 1 year the differences were 2.24% prebronchodilator and 1.48% postbronchodilator (*P*<0.0001 for both) and after 3 years, 1.71%, (*P*<0.0001) and 0.88% (*P*=0.0005). Secondary: Of the 1,241 serious adverse events reported, 162 in the budesonide group and 276 in the placebo group were related to asthma.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			(systemic or inhaled) during the double-blind period; symptom- free days, data on healthcare utilization, days off work, and lost school days	Significantly fewer patients in the budesonide group received additional glucocorticosteroids over time compared with the placebo group (31% versus 45%, respectively; *P*<0.001). An improvement in symptom-free days for both budesonide and placebo groups from baseline was seen over time. However, patients receiving budesonide had significantly more symptom-free days over the 3-year study period (*P*<0.001).
Tinkelman et al[27] Budesonide 100 to 800 µg via DPI depending upon asthma severity	OL for 52 weeks following 2 weeks to 5 months of treatment in one of four DB, PC studies Adults with persistent asthma not receiving corticosteroids (n=249), adults and children previously maintained on ICS (n=356), and adults previously maintained on oral corticosteroids (n=144)	N=1,133 52 weeks	Primary: Percentage of predicted FEV_1, oral corticosteroid use Secondary: Plasma cortisol levels, adverse events	Primary: FEV_1 values continued to improve in all patient populations through week 6 of open-label treatment and were sustained for the remainder of the 52 week study. Patients who had not received prior inhaled corticosteroid treatment demonstrated the greatest improvement in FEV_1 (67.1±18.0% to 81.2±14.8%). Of the 144 oral corticosteroid-dependent patients, 64 entered the open-label study free of oral corticosteroids, and 58 (91%) of those patient remained free of long-term oral corticosteroid use throughout the course of the study. Secondary: There was no evidence of clinically significant suppression of basal or stimulated cortisol levels as a result of treatment with 100, 200, or 400 µg twice daily of budesonide. Basal and stimulated cortisol levels increased by 20.7±183.3 nmol/L and 34.8±283.7 nmol/L, respectively, from baseline to the last observation in patients treated with 800 µg twice daily of budesonide. Thirty-three patients discontinued treatment because of adverse events. Of these patients, the relationship between budesonide therapy and the adverse events was none in 18 patients, unlikely in 4 patients, possible in 8 patients, probably in 1 patient, and highly probable in 2 patients. Ninety-two patients (8%) reported serious adverse events, of which the most commonly reported was asthma exacerbation (30 patients). No substantial or unexpected changes in vital signs were observed.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Study #3031[28] Ciclesonide 80 µg twice daily vs ciclesonide 160 µg every morning vs ciclesonide 80 µg twice daily for 4 weeks then ciclesonide 160 µg every morning for 8 weeks vs placebo	DB, MC, PC, PG, RCT Patients ≥12 years old with a history of persistent asthma for ≥6 months prior to screening and an FEV_1 after 6 hours of SABA withholding of 60% to 85%; therapy was also limited to bronchodilators one month prior to screening	N=691 16 weeks	Primary: Change in morning pre-dose FEV_1 from baseline to the average of weeks 12 and 16 Secondary: Change from baseline to week 16 in morning PEF, change from baseline to week 16 in albuterol utilization, change in asthma symptom score, adverse events	Primary: All three treatment arms showed a statistically significant improvement in FEV_1 scores from baseline to the average of weeks 12 and 16. Change for the 80 µg twice daily group, 0.24 L (P<0.0001). Change for the 160 µg every morning group, 0.12 L (P=0.0021). Change for the 80 µg twice daily then 160 µg every morning group, 0.13 L (P=0.0016). Secondary: All treatment arms showed a statistically significant improvement compared to placebo in change from baseline to week 16 in morning PEF. Change for the 80 µg twice daily group, 36.16 L/min (P<0.0001). Change for the 160 µg every morning group, 23.32 L/min (P=0.0006). Change for the 80 µg twice daily then 160 µg every morning group, 30.71 L/min (P<0.0001). All treatment arms showed a statistically significant improvement compared to placebo in change from baseline to week 16 in albuterol utilization (puffs/day). Change for the 80 µg twice daily group, -0.73 (P<0.0001). Change for the 160 µg every morning group, -0.60 (P=0.0002). Change for the 80 µg twice daily then 160 µg every morning group, -0.41 (P=0.0116). For total asthma symptom score (0 to 5 scale) the treatment difference was statistically significant for the 80 µg twice daily group (-0.57; P=0.0002) and the 80 µg twice daily then 160 µg every morning group (-0.32; P=0.0325). The percentage of patients who experienced treatment emergent adverse events was comparable among treatment groups (twice daily, 55.5%; every morning, 52.8%; twice daily to every morning, 57.8%; placebo, 57.3%). The most common adverse events that occurred in at least 5% of patients for the treatment groups were: aggravated asthma, nasopharyngitis, and headache.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Study #3030[29] Ciclesonide 80 µg twice daily vs ciclesonide 160 µg every morning vs placebo	DB, MC, PC, PG, RCT Patients ≥12 years old with a history of persistent asthma for ≥6 months prior to screening, a documented use of an ICS or an ICS/LABA combination medication for at least 1 month prior to screening, an FEV_1 of 60 to 90% (ICS) or 70 to 95% (ICS/LABA) of predicted normal baseline	N=456 12 weeks	Primary: Change in morning pre-dose FEV_1 from baseline to week 12 Secondary: Change from baseline to week 12 in morning PEF, change from baseline to week 12 in albuterol utilization, change in asthma symptom score, adverse events	Primary: Both treatment arms showed a statistically significant improvement in FEV_1 scores from baseline to week 12. Change for the 80 µg twice daily group, 0.19 L (P<0.0001). Change for the 160 µg every morning group, 0.14 L (P=0.0006). Secondary: Only the 80 µg twice daily treatment arm showed a statistically significant improvement compared to placebo in change from baseline to week 12 in morning PEF. Change for the 80 µg twice daily group, 8.39 L/min (P=0.0349). Change for the 160 µg every morning group, 7.05 L/min (P=0.0769). Both treatment arms showed a statistically significant improvement compared to placebo in change from baseline to week 12 in albuterol utilization (puffs/day). Change for the 80 µg twice daily group, -0.64 (P<0.0001). Change for the 160 µg every morning group, -0.60 (P=0.0002). For the total asthma symptom score (0 to 5 scale) the treatment difference was statistically significant for the 80 µg twice daily group (-0.37; P=0.0011) and the 160 µg every morning group (-0.38; P=0.0010). The percentage of patients who experienced treatment emergent adverse events was comparable among treatment groups (twice daily, 52%; every morning, 57.9%; placebo, 55.3%). The most common adverse events that occurred in at least 5% of patients for the treatment groups were: nasopharyngitis, upper respiratory infection, and pharyngolaryngeal pain.
Bateman et al[30] Ciclesonide 320 µg twice daily vs ciclesonide 640 µg twice	DB, MC, PC, PG, RCT Patients ≥12 years old with a history of persistent asthma for ≥1 year prior to	N=141 12 weeks	Primary: Percent change of oral prednisone dose from baseline to week 12 compared to placebo Secondary: Percentage of patients	Primary: The percentage reduction in oral prednisone dose was statistically significant in both treatment arms; change for the 320 µg twice daily group, -47.39 (P=0.0001). Change for the 640 µg twice daily group, -62.54 (P=0.0001). Change for the placebo group, 4.21. Secondary: The percentage of patients who were able to eliminate their prednisone

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
daily vs placebo	screening. Were also corticosteroid dependant with severe asthma and use of oral prednisone at least every other day for 5 to 6 months prior to screening with a history of ICS during the 6 months prior to screening and required use of a β_2-agonist for asthma control with the 2 weeks prior to screening, an FEV_1 between 40 to 80% of predicted normal following a 6 hour β_2-agonist treatment withholding period		who were able to completely discontinue prednisone use, change from baseline to week 12 in morning pre-dose FEV_1, change from baseline to week 12 in morning PEF, change from baseline in albuterol utilization, change in asthma symptom score, assessment of HPA-axis suppression, adverse events	usage was statistically significant in both treatment groups when compared to placebo. In the 320 µg twice daily group the percentage was 29.8 (*P*=0.0386), 31.3 (*P*=0.0233) in the 640 µg twice daily group, and 11.1 in the placebo group. Both treatment arms showed a statistically significant improvement in FEV_1 scores when compared to placebo from baseline to week 12. Change for the 320 µg twice daily group, 0.17 L (*P*=0.0237). Change for the 640 µg twice daily group, 0.17 L (*P*=0.0277). Neither treatment arm showed a statistically significant improvement in PEF scores when compared to placebo from baseline to week 12. Change for the 320 µg twice daily group, 5.02 L/min (*P*=0.5803). Change for the 640 µg twice daily group, 16.67 L/min (*P*=0.0736). Neither treatment arms showed a statistically significant improvement compared to placebo in change from baseline to week 12 in albuterol utilization (puffs/day). Change for the 320 µg twice daily group, -0.39 (*P*=0.5854). Change for the 640 µg twice daily group, -0.40 (*P*=0.5806). For total asthma symptom score (0 to 5 scale) the treatment difference was not statistically significant for either treatment group. Change for the 320 µg twice daily group, 0.33 (*P*=0.2669). Change for the 640 µg twice daily group, -0.07 (*P*=0.8197). At baseline the percentage of patients with suppressed HPA-axis was 66.0%, 60.4%, 62.2% and at week 12 it was 46.8%, 43.8%, 53.3% in the 320 µg twice daily group, 640 µg twice daily group, and placebo group respectively. The percentage of patients who experienced treatment emergent adverse events was comparable among treatment groups (320 µg, 85.1%; 640 µg, 79.6%; placebo, 88.9%). The most common adverse event that occurred in at least 5% of patients for the treatment groups were: aggravated asthma, upper respiratory infection, headache, sinusitis, and nasopharyngitis.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Study #321[31] Ciclesonide 80 µg every morning vs ciclesonide 160 µg every morning vs ciclesonide 320 µg every morning vs placebo	DB, MC, PC, RCT Patients were ≥12 years old with mild to moderate persistent asthma for 6 months prior and were nonsmokers for at least 1 year, an FEV_1 of 60 to 85% predicted normal with a reversibility of FEV_1 by ≥12% after 2 albuterol inhalations	N=526 12 weeks	Primary: Change from baseline to week 12 in morning pre-dose FEV_1 compared to placebo Secondary: Change from baseline to week 12 in morning PEF, change from baseline to week 12 in albuterol utilization, change in asthma symptom score, change in AQLQ score, adverse events	Primary: Two of the three treatment arms showed a statistically significant improvement versus placebo in FEV_1 scores. Change for the 80 µg group, 0.12 L (*P*=0.0123). Change for the 160 µg group, 0.07 L (*P*=0.1645). Change for the 320 µg group, 0.15 L (*P*=0.0014). Secondary: All treatment arms showed a statistically significant improvement versus placebo in change from baseline to week 12 in morning PEF. Change for the 80 µg group, 15.58 L/min (*P*=0.0032). Change for the 160 µg group, 18.93 L/min (*P*=0.0004). Change for the 320 µg group, 24.53 L/min (*P*=0.0001). All treatment arms showed a statistically significant improvement compared to placebo in change from baseline to week 12 in albuterol utilization (puffs/day). Change for the 80 µg group, -1.52 (*P*=0.0001). Change for the 160 µg group, -1.60 (*P*=0.0001). Change for the 320 µg group, -1.88 (*P*=0.0001). For total asthma symptom score (0 to 5 scale) the treatment difference was statistically significant for all three groups. Change for the 80 µg group, -0.38 (*P*=0.0146). Change for the 160 µg group, -0.55 (*P*=0.0006). Change for the 320 µg group, -0.68 (*P*=0.0001). The overall score and two of the four domains in the AQLQ (symptoms and emotional function) were statistically significantly improved in all 3 treatment arms (*P* value not reported). The percentage of patients who experienced treatment emergent adverse events was comparable among treatment groups (80 µg, 57.1%; 160 µg, 50.8%; 320 µg, 50.4%; placebo, 53.7%). The most common adverse event that occurred in at least 5% of patients for the treatment groups was nasopharyngitis and upper respiratory tract infection.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Study #322[32] Ciclesonide 80 µg every morning vs ciclesonide 160 µg every morning vs ciclesonide 320 µg every morning vs placebo	DB, MC, PC, RCT Patients ≥12 years old with mild to moderate persistent asthma for 6 months prior and were nonsmokers for at least 1 year, an FEV_1 of 60 to 85% predicted normal with a reversibility of FEV_1 by ≥12% after 2 albuterol inhalations	N=489 12 weeks	Primary: Change from baseline to week 12 in morning pre-dose FEV_1 compared to placebo Secondary: Change from baseline to week 12 in morning PEF, change from baseline to week 12 in albuterol utilization, change in asthma symptom score, change in AQLQ score, adverse events	Primary: All three treatment arms showed a statistically significant improvement versus placebo in FEV_1 scores from baseline to the week 12. Change for the 80 µg group, 0.12 L (*P*=0.0224). Change for the 160 µg group, 0.19 L (*P*=0.0003). Change for the 320 µg group, 0.12 L (*P*=0.0173). Secondary: Two of the three treatment arms showed a statistically significant improvement versus placebo in change from baseline to week 12 in morning PEF. Change for the 80 µg group, 9.27 L/min (*P*=0.0871). Change for the160 µg group, 26.8 L/min (*P*=0.0001). Change for the 320 µg group, 12.89 L/min (*P*=0.0171). All treatment arms showed a statistically significant improvement compared to placebo in change from baseline to week 12 in albuterol utilization (puffs/day). Change for the 80 µg group, -1.03 (*P*=0.0002). Change for the 160 µg group, -1.24 (*P*=0.0001). Change for the 320 µg group, -1.01 (*P*=0.0002). For total asthma symptom score (0 to 5 scale) the treatment difference was statistically significant for two of the three groups. Change for the 80 µg group, -0.46 (*P*=0.0060). Change for the 160 µg group, -0.52 (*P*=0.0020). Change for the 320 µg group, -0.25 (*P*=0.1346). The overall score and three of the four domains in the AQLQ (symptoms, activity, limitation and emotional function) were statistically significantly improved in all 3 treatment arms (*P* value not reported). The percentage of patients who experienced treatment emergent adverse events was comparable among treatment groups (80 µg, 62.1%; 160 µg, 65.9%; 320 µg, 65.3%; placebo, 66.9%).The most common adverse event that occurred in at least 5% of patients for the treatment groups was nasopharyngitis, headache and upper respiratory tract infection.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Busse et al[33] Beclomethasone HFA 100 µg/day vs beclomethasone HFA 400 µg/day vs beclomethasone HFA 800 µg/day vs beclomethasone CFC 100 µg/day vs beclomethasone CFC 400 µg/day vs beclomethasone CFC 800 µg/day	DB, MC, PG, RCT Asthmatic subjects who had deteriorated in their asthma control after discontinuation of ICS	N=323 6 weeks	Primary: Change from baseline in FEV_1 percent predicted at week 6 Secondary: Percent change from baseline in $FEF_{25-75\%}$, FVC, morning and evening PEF, asthma symptom scores, nighttime awakenings, daily albuterol use	Primary: For each treatment group, FEV_1 percent predicted increased over the first 4 weeks of treatment and tended to reach a plateau by week 6. Change from baseline at week 6 in FEV_1 percent predicted was greater with 800 µg/day beclomethasone HFA (-32.7%; *P*=0.049) than 400 µg /day (-25.1%) and marginally, but not significantly greater (*P*=0.09) with 800 µg /day (-31.3%) of the beclomethasone CFC than 400 µg/day (-22.6%). Secondary: ANOVA showed significant dose effects across both products for $FEF_{25-75\%}$, FVC, and morning PEF. Evening PEF, asthma symptom scores, nighttime sleep disturbances, and daily albuterol use were similar in all treatment groups.
Brenner et al[34] At discharge, all patients were given prednisone 40 mg/day for 5 days and inhaled β_2-agonists as needed and were	PC, RCT Patients aged 18 to 50 years old with a diagnosis of asthma presenting to the emergency	N=104 24 days	Primary: PEFR Secondary: Overall symptoms and albuterol use	Primary: PEFR was similar between the two groups throughout the trial (*P*=0.36 on day 24). There was a mean difference of 4 units, favoring flunisolide, between the groups. Secondary: Both symptoms and albuterol use were similar in both groups for the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
randomly assigned to receive high-dose inhaled flunisolide (2 mg/day) or placebo.	department with an acute asthma exacerbation			duration of the trial. 75% of patients in the flunisolide group reported symptom improvement vs 70% in the placebo group (95% CI, -17 to 27).
Lee-Wong et al[35] Flunisolide 2,000 µg twice daily via spacer vs placebo twice daily via spacer Patients were also randomized to receive oral prednisone or placebo.	DB, PC, RCT Patients aged 18 to 55 years admitted to the emergency department for an acute asthma exacerbation	N=40 7 days	Primary: PEFR, FEV_1 Secondary: Change in asthma symptom scores	Primary: From day 1 to day 7, mean PEFR increased from 190 to 379 L/min in the ICS group, and from 207 to 347 L/min in the prednisone (*P*=0.95; 95% CI, -66.3 to ∞). Mean FEV_1 increased from 1.6 to 2.3 L in the ICS group and from 1.4 to 2.1 L in the prednisone group (*P*=0.33; 95% CI, -21.7 to ∞). Secondary: Mean symptom scores declined from 1.4 to 0.7 in the ICS group and decreased from 1.3 to 0.4 in the prednisone group (*P*=0.39; 95% CI, -0.4 to ∞).
Nelson et al[36] Fluticasone 500 µg twice daily vs fluticasone 1,000 µg twice daily vs placebo twice daily	DB, PC, PG, RCT Male and female patients 12 years of age or older with chronic asthma diagnosed according to the American Thoracic Society criteria and receiving oral corticosteroid treatment over the preceding 6 months	N=111 16 weeks	Primary: Percentage of patients with a change in maintenance prednisone dose, mean change from baseline in maintenance dose of prednisone Secondary: Changes in FEV_1, patient-measured morning and evening PEF, patient-rated asthma symptoms, number of nighttime awakenings requiring albuterol	Primary: At study end point, oral prednisone use was eliminated by 75% and 89% of patients treated twice daily with 500 or 1,000 µg of fluticasone, respectively, compared with 9% in the placebo group. Mean maintenance dose of oral prednisone decreased significantly in both fluticasone groups compared with placebo, with decreases of 12.0 mg and 13.0 mg in the 500 and 1,000 µg groups, respectively, compared with 5.2 mg in the placebo group (*P*<0.001). Secondary: Changes in FEV_1 were significantly greater in both the fluticasone 500 µg group (8.37±3.84) and the 1,000 µg group (24.21±5.67) vs placebo (0.56±5.56; *P*≤0.05 for all). Both morning and evening PEF improved in the fluticasone 500 µg (23+10 morning, 3±7 evening) and 1,000 µg (67±12 morning, 48±10 evening). The placebo group did not improve (-23±11 morning and -9±12 evening;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				$P \leq 0.05$ for all). Asthma symptom scores improved in both the fluticasone 500 µg (-0.26±0.08) and the 1,000 µg groups (-0.47±0.13; $P \leq 0.05$); symptom scores worsened in the placebo group (0.26±0.12; $P \leq 0.05$). Nighttime awakenings requiring albuterol decreased in both the fluticasone 500 µg (-0.19±0.11) and the 1,000 µg groups (-0.42±0.13); nighttime awakenings increased in the placebo group (0.26±0.15; $P \leq 0.05$ for all).
Fish et al[37] Mometasone 400 µg to 800 µg twice daily vs placebo	MC, PC, RCT Patients with severe persistent, oral corticosteroid-dependent asthma	N=132 12 weeks, followed by 9 month open-label phase	Primary: Percentage change in daily oral corticosteroid prednisone requirement Secondary: Spirometric measurements (FEV_1, FVC, forced expiratory flow, midexpiratory phase), morning and evening PEF, rescue albuterol use, asthma symptom scores, number of nocturnal awakenings caused by asthma that required albuterol use, and general and asthma-specific quality-of-life measures	Primary: Oral corticosteroid requirements were reduced by 46.0% for the mometasone 400 µg twice daily group and 23.9% for mometasone 800 µg twice daily group compared with the placebo group that had an increase in oral corticosteroid requirements by 164.4% ($P<0.01$). Oral corticosteroid requirements were eliminated in 40%, 37%, and 0% of the patients after 12 weeks and 71%, 62%, and 58% at the end of the 9 month open-label phase in the mometasone 400 µg and 800 µg twice daily and placebo groups, respectively. Secondary: Nocturnal awakenings fell by 57% and 66% in the mometasone 400 and 800 µg twice daily groups, respectively and increased by 62% in the placebo group ($P<0.01$). Daily rescue medication use was significantly reduced in the mometasone 400 µg group ($P<0.01$), but not in the mometasone 800 µg group when compared with placebo. All other secondary endpoints did not exhibit any statistically differences between the active treatment groups.
Aalderen et al[38] Beclomethasone 200 µg/day via HFA MDI	DB, DD, PG, RCT Patients 5 to 12 years of age with an asthma	N=139 18 weeks	Primary: Morning PEF percent predicted	Primary: Mean change from baseline in morning PEF percent predicted was 5.7% in the beclomethasone group and 7.3% in the fluticasone group. The treatment difference was -1.9 (90% CI, -4.9 to 1.0; *P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs fluticasone 200 µg/day via CFC MDI During weeks 7 to 12 and 13 to 18 patients were stepped down to 100 and 50 µg/day respectively if they were achieving good control. Those with poor control discontinued the study, and those labeled as intermediate did not have a dose change.	diagnosis of at least 3 months, PEF ≥ 60% of predicted normal, and who are currently using a SABA on an as-required basis		Secondary: Evening PEF percent predicted, FEV_1 percent predicted, FVC percent predicted, symptom-free days, nights without sleep disturbances, use of a β_2-agonist, asthma control, QOL, adverse events	Secondary: Mean change from baseline in evening PEF% predicted was 5.9% in the beclomethasone group and 7.3% in the fluticasone group. The treatment difference was -1.5 (90% CI, -4.6 to 1.6; *P*=0.415). Mean change from baseline in FEV_1 percent predicted was 3% in the beclomethasone group and 0.6% in the fluticasone group. The treatment difference was 1.6 (*P*=0.335). Mean change from baseline in FVC percent predicted was 5.3% in the beclomethasone group and 0.4% in the fluticasone group. The treatment difference was 4.6 (*P*=0.084). The percentage change from baseline of symptom-free days was 35.2% in both treatment groups (*P*=0.897). The percentage change in nights without sleep disturbances was 17.5% and 20.8% in the beclomethasone group and fluticasone group respectively (*P*=0.561*).* The mean number of puffs of a β_2-agonist decreased from 1.59 to 0.73 puffs/day in the beclomethasone group, and from 1.40 to 0.69 puffs/day in the fluticasone group (*P*=0.505). At week-6, 36% of patients in the beclomethasone group and 42% in the fluticasone group had good asthma control and were able to step down in their respective doses to 100 µg/day. At week-12 another step down therapy to 50 µg/day was possible in 66% and 61% of the patients in the beclomethasone and fluticasone group respectively. The proportion of patients with a clinically significant improvement in asthma QOL was similar in both groups (*P*=0.369). There were no statistically significant differences in the proportion of patients experiencing adverse events in the beclomethasone (47%) and fluticasone (49%) groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Raphael et al[39] Beclomethasone 168 µg twice daily vs beclomethasone 336 µg twice daily vs fluticasone 88 µg twice daily vs fluticasone 220 µg twice daily	DB, PG, RCT Nonsmoking males and females aged 12 years or older with an established diagnosis of chronic asthma requiring daily ICS therapy for at least 6 months before the study	N=399 14 weeks	Primary: Changes in morning predose FEV_1 Secondary: $FEF_{25-75\%}$, FVC, morning and evening PEF, probability of remaining in the study, albuterol use, nighttime awakenings, asthma symptoms	Primary: The FEV_1 for all treatment groups improved with respect to baseline; however, a significant drug effect was observed in favor of fluticasone compared with beclomethasone in the mean change in FEV_1 from baseline to endpoint (0.31 L to 0.36 L vs 0.18 L to 0.21 L; P=0.006). At endpoint, mean FEV_1 values in the low-and medium-dose fluticasone treatment groups improved by 0.31 L (14%) and 0.36 L (15%) respectively, compared with improvements of 0.18 L (8%) and 0.21 L (9%) in the low-and medium-dose beclomethasone treatment groups, respectively. Secondary: Forced expiratory flow ($FEF_{25-75\%}$) and FVC were improved from baseline in all treatment groups; fluticasone showed greater improvements than beclomethasone ($P \leq 0.034$). Fluticasone provided significantly greater improvement in morning PEF when compared with beclomethasone treatment at endpoint and in all of the other time points except week 2 (P<0.004). The fluticasone group also experienced a significant improvement in morning PEF relative to baseline (15.8 L to 22.8 L), but the beclomethasone groups did not (0.7 L to 7.2 L). A similar trend was seen in evening PEF, but the improvement observed in response to fluticasone compared with beclomethasone did not achieve statistical significance. There were no significant differences noted in the analysis of the probability of remaining in the study. The percentage of days in which no albuterol was used was significantly higher with fluticasone treatment than with beclomethasone (P=0.01 at endpoint). Albuterol use declined by 0.9 (26%) and 0.5 (16%) puffs/day in the low and moderate fluticasone treatment groups, respectively, whereas it was unchanged in the beclomethasone low-dose group and decreased by 0.3 (9%) puffs/day in the moderate-dose group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There were no significant differences noted in the analysis of nighttime awakenings. Significant drug effects were observed at endpoint in favor of fluticasone for asthma symptom scores (*P*=0.024) and in the percentage of days in which no symptoms were recorded (*P*=0.027).
Sharek et al[40] Beclomethasone 328 to 400 µg/day vs fluticasone 200 µg/day	MA 1966 to 1998, DB, RCT studies that evaluated linear growth in children ages 6 to 16 years of age with asthma and concomitant ICS therapy	N=855 (5 studies)	Primary: Linear growth velocity in cm/year Secondary: None reported	Primary: Each of the four trials that evaluated beclomethasone revealed a decreased linear growth velocity, and the MA of these four trials concluded that there was a significant decrease in linear growth in children using beclomethasone for mild-moderate asthma. The WMD between 231 patients using beclomethasone compared to 209 being treated with a non-steroid medication was -1.51 cm/year (95% CI, -1.15 to -1.87). For the fluticasone study the mean difference between 96 children treated with fluticasone and 87 treated with placebo was -0.43 cm/year (95% CI, -0.01 to -0.85; *P* value not reported). Secondary: None reported
Nathan et al[41] Beclomethasone 168 µg twice daily vs mometasone 100 µg twice daily vs mometasone 200 µg twice daily vs	DB, DD, MC, PC, RCT Patients with moderate persistent asthma previously maintained on ICS	N=227 12 weeks	Primary: Changes in FEV_1 Secondary: PEFR, asthma symptoms, nocturnal awakenings, albuterol use	Primary: FEV_1 significantly improved for all three active treatment groups compared with placebo (*P*<0.01). There was no statistical significant difference in FEV_1 between the treatment groups mometasone 200 µg and beclomethasone µg (*P*=0.07) or mometasone 200 µg and mometasone 100 µg (*P*=0.08). Secondary: Improvement in FEV_1, PEFR, asthma symptoms, nocturnal awakenings, and albuterol use were approximately twice as large for the mometasone 200 µg group as the response for mometasone 100 µg and beclomethasone group, but did not reach statistical significance.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo				
Bernstein et al[42] Beclomethasone 168 µg twice daily vs mometasone 100 µg twice daily vs mometasone 200 µg twice daily vs mometasone 400 µg twice daily vs placebo	DB, DD, MC, RCT Patients with asthma previously being treated with ICS	N=365 12 weeks	Primary: Mean change from baseline to endpoint for FEV_1 Secondary: FVC, $FEF_{25\%-75\%}$, PEFR, patient evaluation of asthma symptoms, physician evaluation of asthma symptoms	Primary: The difference in FEV_1, FVC, $FEF_{25\%-75\%}$, and PEFR from baseline was significantly greater in all the active treatment groups compared with placebo ($P<0.01$). The mometasone 200 µg twice daily group showed greater improvement than mometasone 100 µg twice daily group, with the mometasone 400 µg twice daily group showing no additional benefit. Secondary: Changes in lung function from baseline for the mometasone 100 µg twice daily group and beclomethasone 168 µg twice daily group were similar. Asthma symptoms as evaluated subjectively by patients and physicians were similarly improved for the mometasone 200 ($P<0.01$) and 400 ($P=0.05$) µg twice daily groups, which were slightly better than that of the mometasone 100 µg twice daily ($P=0.01$) and beclomethasone 168 µg twice daily ($P=0.02$) groups.
Bronsky et al[43] Beclomethasone 336 µg/day vs triamcinolone 800 µg/day vs	DB, DD, MC, PC, PG, RCT Adults with mild to moderately severe asthma maintained on ICS	N=328 56 days	Primary: Mean changes in FEV_1 from baseline Secondary: Asthma symptom scores, average use of albuterol, nighttime awakenings, mean change from baseline in $FEF_{25-75\%,}$ and FVC	Primary: Throughout the study, mean change and percent mean change in FEV_1 for both active treatment groups were significantly greater than placebo (0.27 L for beclomethasone, 0.16 L for triamcinolone, and -0.10 L for placebo; $P\leq0.01$). A pairwise comparison showed that mean percent change and mean change (SD) were consistently greater in the beclomethasone group throughout the study, with the difference statistically significant at day 28 ($P=0.042$ and $P=0.036$, respectively). Both active treatments were better than placebo ($P\leq0.003$).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo				Secondary: At each visit and at study endpoint, mean reductions in total symptom severity scores were significantly greater in the beclomethasone group compared with the triamcinolone group (*P*=0.028) and at endpoint in both active treatment groups compared with placebo (-1.37, -0.58, 0.83; *P*<0.001). The mean average daily use of albuterol calculated weekly tended to be least in the beclomethasone group (2.86), greatest in placebo group (4.43), and intermediate in triamcinolone group (3.61). Nighttime awakenings were not significantly different among the treatment groups. Mean change from baseline in $FEF_{25-75\%,}$ and FVC showed both active treatment groups better than placebo, with beclomethasone being clinically better than triamcinolone throughout the study.
Berkowitz et al[44] Beclomethasone 336 µg/day and triamcinolone placebo vs triamcinolone 800 µg/day and beclomethasone placebo vs triamcinolone and beclomethasone placebo	DB, DD, PC, RCT Patients aged 18 to 65 years of age with a documented history of bronchial asthma	N=339 56 days	Primary: Change from baseline in FEV_1 Secondary: $FEF_{25-75\%}$, PEFR, and FVC	Primary: For both active treatment groups, increases in baseline FEV_1 were evident at all time points; these results were statistically significant when compared to placebo (*P*<0.05). At end point, FEV_1 had increased by 10.3% in the beclomethasone group and 11.2% in the triamcinolone group (*P*≤0.05 vs placebo). Secondary: Mean increases in $FEF_{25-75\%}$ and PEFR were similar in both active treatment groups. The same trend was noticed for FVC. All results were numerically and statistically significant when compared to placebo (*P*<0.05).
Newhouse et al[45] Beclomethasone 750 µg,	MC, PG, RCT Patients with	N=176 6 weeks	Primary: Change in prebronchodilator FEV_1	Primary: There were no statistically significant differences between the two treatment groups in the changes in FEV_1 during the six week treatment

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
twice daily via AeroChamber® for a two week run-in period then randomized to: budesonide 600 µg twice daily via Turbuhaler® vs flunisolide 750 µg twice daily via AeroChamber®	moderate asthma (FEV_1 of 40% to 85% of predicted)		from week 0 to week 6, change in mean albuterol usage during the weeks preceding week 0 and week 6 Secondary: Changes in PEF, asthma scores, nocturnal awakenings	period (difference of -0.031 L in percent predicted favoring flunisolide; *P*=0.544). There were also no significant changes in albuterol use between the two groups (difference of 0.261 puffs/day favoring budesonide; *P*=0.333). Secondary: There were no statistically significant differences between the two treatment groups in the change in PEF, asthma symptoms scores, and nocturnal awakenings during the treatment period.
Vermeulen et al[46] Budesonide 800 µg every evening vs ciclesonide 320 µg every evening	DB, DD, MC, PG, RCT Patients 12 to 17 years of age with severe asthma for 6 months with an FEV_1 of >50% and <80% who were not controlled with budesonide 400 µg/day for ≥4 weeks prior to study	N=403 12 weeks	Primary: Change in evening pre-dose FEV_1 from baseline to week 12, percentage of days without asthma symptoms and without use of rescue medication Secondary: Change in FEV_1 percent of predicted, change in FVC from baseline to week 12, percentage of patients experiencing an asthma exacerbation, change in morning PEF from baseline to week 12, change in asthma symptom score, change from baseline to week 12 in albuterol utilization, change in	Primary: At week 12 significant increases in FEV_1 were seen in both treatment arms. Ciclesonide 320 µg every evening, 0.505 L (*P*<0.0001). Budesonide 800 µg every evening, 0.536 L (*P*<0.0001). There were no significant differences between treatment groups (*P*=0.076). Percentage of days without asthma symptoms and without use of rescue medication was 84% in the ciclesonide group and 85% in the budesonide group (*P* value not reported). Secondary: FEV_1 percent predicted increased in the ciclesonide group from 73.1percent at baseline to 89.4% at the end of the study. In the budesonide group FEV_1% predicted was 73.0% at baseline and 90.7% at the end of the study. There was no significant difference between the two study groups (*P* value not reported). For FVC the change from baseline was significant in both treatment groups with 0.433 L in the ciclesonide group and 0.472 L in the budesonide group. The difference between the two treatment groups was not significant (*P*=0.080). Asthma exacerbations were reported in 2.6% of the patients in the ciclesonide treatment group and 1.5% in the budesonide group. There was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			PAQLQS score, adverse events	no significant difference between the two treatment groups (*P* value not reported). Morning PEF increased from baseline to week 12 by 8.0 L/min in the ciclesonide treatment arm (*P*=0.0424) and 4.9 L/min in the budesonide treatment arm, which was not statistically significant (*P* value not reported). Asthma symptom scores (0 to 5 scale) were significantly reduced in both treatment groups. Ciclesonide 320 µg every evening, -0.07 (*P*<0.0005). Budesonide 800 µg every evening, -0.14 (*P*<0.0001). There were no significant differences between treatment groups (*P* value not reported). The median use of rescue medication at week 12 was reduced to zero puffs per day in both the ciclesonide treatment group (*P*<0.0001) and the budesonide group (*P*=0.0003). Overall PAQLQS scores (1 to 7 scale) were improved in both treatment groups. Ciclesonide 320 µg every evening, 0.19 (*P*=0.0001). Budesonide 800 µg evening, 0.18 (*P*=0.0056). The percentage of patients who experienced treatment emergent adverse events was comparable among treatment groups (320 µg, 26.5%; 800 µg, 18.3%). The most common adverse event that occurred in at least 5% of patients for either treatment groups was pharyngitis (ciclesonide, 5.9%; budesonide, 3.8%).
Von Berg et al[47] Budesonide 400 µg every evening vs ciclesonide 160 µg every evening	DB, DD, MC, PG, RCT Patients 6 to 11 years old with persistent asthma for ≥6 months	N=621 12 weeks	Primary: Change in FEV_1 from baseline to week 12 Secondary: Change in morning PEF from baseline to week 12, change in asthma symptom score, change from baseline to week 12 in rescue medication	Primary: At week 12 significant increases in FEV_1 compared to baseline were seen in both treatment arms. Ciclesonide 160 µg every evening, 0.232 L (*P*<0.0001). Budesonide 400 µg every evening, 0.250 L (*P*<0.0001). Ciclesonide proved to be non-inferior to budesonide with no significant differences between treatment groups (*P*=0.8158). Secondary: Treatment with both groups achieved a statistically significant increase in morning PEF compared to baseline. Ciclesonide 160 µg every evening, 22.5 L/min (*P*<0.0001). Budesonide 400 µg every evening, 26.3 L/min

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			utilization, percentage of days without asthma symptoms and without need for rescue medication, percentage of patients with asthma exacerbations, change in PAQLQS and PACQLQ score, adverse events, body height increase at week 12, change in 24-hour urinary cortisol	(*P*<0.0001).There were no significant differences between treatment groups (*P*=0.8531). Both treatment arms achieved a statistically significant improvement in asthma symptom score (0 to 5 scale) after 12 weeks of treatment. Ciclesonide 160 µg every evening, -1.21 (*P*<0.0001). Budesonide 400 µg every evening, -1.21 (*P*<0.0001). There were no significant differences between treatment groups (*P*=0.8379). Both treatment arms achieved a statistically significant improvement in the need for rescue medication after 12 weeks of treatment. Ciclesonide 160 µg every evening, -1.58 (*P*<0.0001). Budesonide 400 µg every evening, -1.64 (*P*<0.0001). There were no significant differences between treatment groups (*P*=0.8593). The percentage of days without asthma symptoms and without need for rescue medication was 73% in the ciclesonide 160 µg treatment group, and 70% in the ciclesonide 400 µg group, and in the budesonide treatment group (*P* value not reported). The percentage of patients with asthma exacerbations was 2.6% in the ciclesonide 160 µg group, and 1% in the budesonide treatment group (*P* value not reported). Both treatment arms achieved a statistically significant improvement in overall PAQLQS (1 to 7 scale) and PACQLQ scores compared to baseline after 12 weeks of treatment. For PAQLQS and PACQLQ the scores (0.69, 0.88) and (0.70, 0.96) for the ciclesonide 160 µg every evening and budesonide 400 µg every evening respectively were statistically significant (*P*<0.0001). The percentage of patients who experienced treatment emergent adverse events was 38% among both treatment groups. The most common adverse events that occurred in at least 5% of patients for either treatment groups were: pharyngitis: (5.9%, 3.8%), nasopharyngitis: (4.1%, 5.4%), and upper respiratory tract infection, (3.6%, 6.3%) for the ciclesonide and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				budesonide groups respectively. The frequency of oropharyngeal adverse events was low in both treatment groups (0.2%, 1.5%) for the ciclesonide 160 µg every evening and budesonide 400 µg every evening respectively. At week 12 the body height increased by 1.18 cm in the ciclesonide group and by 0.70 cm in the budesonide group. Both of these values were significant when compared to baseline (*P*<0.0001). The increase in height was significantly greater in the ciclesonide group than in the budesonide group (*P*=0.0025). Treatment with ciclesonide and budesonide resulted in significant decreases of urinary cortisol (nmol/mmol creatinine). Ciclesonide 160 µg every evening, -2.17 (*P*<0.0001). Budesonide 400 µg every evening, -5.16 (*P*<0.0001). The difference between these two treatment groups was significant (*P*<0.0001).
Ferguson et al[48] Budesonide 200 µg twice daily via DPI vs fluticasone 100 µg twice daily via DPI	DB, DD, MC, PG, RCT Children 6 to 9 years of age with persistent asthmas ≥6 months, and an FEV≥60% predicted, with height between the 5th and 95th centiles for the patients' age and run-in growth velocity between the 20th and 95th percentiles	N=400 12 months	Primary: Growth velocity Secondary: PEFR, FEV_1, exacerbations, symptoms-free days and nights, salbutamol-free nights, adverse events	Primary: Mean growth velocity from baseline to week 52 was 5.5 cm/year in the fluticasone group and 4.6 cm/year in the budesonide group. This difference of 0.9 cm/year was statistically significant (*P*<0.001).The difference in growth velocities increased over the 12 months. The majority of patients in the fluticasone group grew 5.0 to 7.0 cm/year whereas in the budesonide group patients grew 3.0 to 5.0 cm/year. Secondary: Change in morning PEFR was 29.7 L/min, and 26.2 L/min for the fluticasone and budesonide groups respectively. There was no statistically significant difference between the two treatment groups (*P*=0.460). Change in FEV_1 was 0.19 L, and 0.25 L for the fluticasone and budesonide groups respectively. There was no statistically significant difference between the two treatment groups (*P*=0.154). Patients with no exacerbations were 75% and 68% for the fluticasone and budesonide groups respectively. There was no statistically significant difference between the two treatment groups (*P*=0.131).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Patients with 100% symptom-free days were 49% and 48% for the fluticasone and budesonide groups respectively. There was no statistically significant difference between the two treatment groups (*P*=0.799). Patients with 100% symptom-free nights were 50% and 58% for the fluticasone and budesonide groups respectively. There was no statistically significant difference between the two treatment groups (*P*=0.232). Patients with 100% salbutamol-free nights were 57% and 52% for the fluticasone and budesonide groups respectively. There was no statistically significant difference between the two treatment groups (*P*=0.180). Adverse events were reported in 81% and 71% in the fluticasone and budesonide groups respectively. However only 3% and 2% of these events were considered to be treatment related. Serious adverse events were reported in <1% and 3% in the fluticasone and budesonide groups respectively.
Ferguson et al[49] Budesonide 400 µg twice daily via DPI vs fluticasone 200 µg twice daily via DPI	DB, DD, PG, RCT Children ages 4 to 12 years with a history of moderate to severe asthma who required moderate to high doses of ICS to control symptoms for at least 1 month preceding the start of the run in period	N=442 22 weeks	Primary: Mean morning PEF during the last 7 treatment days, obtained from the daily record cards assessed by ANOVA Secondary: Adverse events	Primary: The adjusted mean morning PEF, measured over the last 7 treatment days, were 271±82 and 259±75 L/min, for the fluticasone and budesonide treatment groups, respectively. The difference in means was 12 L/min (90% CI, 6 to 19 L/min; *P*=0.002). For the purpose of this study, the two treatment regimens were considered to be equivalent if the 90% CI for the difference in mean morning PEFs for the last 7 days of the 20-week treatment period was within ± 15 L/min. The 90% upper and lower confidence limits for the treatment difference were 6 and 9 L/min, respectively, indicating that the treatments were not equivalent, with fluticasone showing improved outcomes. Secondary: There was no significant difference in the number of children who experienced an adverse event in the 2 treatment groups.
Fitzgerald et al[50] Budesonide 750 µg twice	DB, RCT, XO Children ages 5 to	N=30 12 weeks	Primary: The daily mean morning and evening PEF and	Primary: Although the trend favored fluticasone, there was no statistically significant difference between the treatment groups PEF and symptoms scores.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
daily vs fluticasone 375 µg twice daily	16 years with persistent severe asthma (requiring 1,000 to 2,000 µg/day of inhaled beclomethasone or budesonide) continuously for symptom control over the previous 12 months		day and night symptom scores Secondary: Physician/patient/parent assessment of efficacy, total number of exacerbations requiring systemic steroids, adrenal function, growth, adverse events	Secondary: There was no difference in physician or patient/parent assessment of efficacy with 90% rating both fluticasone and budesonide effective or very effective. The total number of exacerbations (fluticasone=33, budesonide=35) and those exacerbations requiring systemic steroids (fluticasone=9, budesonide=11) suggested no difference between the treatment groups. There were no significant differences in adjusted means for urinary free cortisol levels at 8 or 12 weeks, ACTH levels, or baseline and peak serum cortisol levels between the treatment phases. There was no significant treatment effect on growth which remained normal in either group. Most of the adverse events were related to exacerbations of asthma or upper respiratory tract infections in both groups. There was no difference in either the total number of adverse events or the number of adverse events considered possibly related to inhaled corticosteroids between the treatment groups.
Bousquet et al[51] Budesonide 400 µg twice daily vs mometasone 100, 200, or 400 µg twice daily	DB, MC, RCT Patients with moderate persistent asthma previously maintained on daily ICS	N=730 12 weeks	Primary: Mean change from baseline to endpoint FEV_1 Secondary: Self-rated asthma symptom scores, nocturnal awakenings requiring albuterol use as rescue medication, daily albuterol use, physician evaluation of response to therapy	Primary: FEV_1 was significantly improved in the mometasone 200 and 400 µg twice daily treatment group compared with the budesonide 400 µg twice daily treatment group ($P<0.05$). Secondary: The morning wheezing scores were significantly improved in the mometasone 400 µg twice daily group compared with the budesonide 400 µg twice daily group or mometasone 100 µg twice daily group (*P* value not reported). Patients treated with mometasone 200 and 400 µg twice daily required significantly less albuterol than did patients treated with budesonide 400 µg twice daily.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Physicians reported a significant improvement in asthma symptoms scores in the mometasone 400 and 200 µg twice daily group compared with budesonide group (63% and 65% vs 50%; *P* value not reported).
Corren et al[52] Budesonide 400 µg once daily vs mometasone 440 µg once daily vs placebo	DB, DD, MC, PC, RCT Patients with moderate persistent asthma previously using twice daily ICS	N=262 8 weeks	Primary: Percent change in FEV_1 from baseline to endpoint Secondary: Morning and evening PEFR, FVC, $FEF_{25\%-75\%}$, albuterol use, percentage of asthma symptom-free days, nocturnal awakenings due to asthma, physician-evaluated response to therapy, asthma symptom scores	Primary: The percent change in FEV_1 was significantly greater in the mometasone group compared with the budesonide group ($P<0.01$) and placebo group ($P<0.001$). Secondary: Pulmonary function ($FEF_{25\%-75\%}$, FVC), evening asthma symptoms scores, albuterol use, percentage of asthma symptom-free days, and physician-evaluated response to therapy were significantly improved in the mometasone group compared with both the budesonide and placebo groups ($P<0.05$).
Weiss et al[53] Budesonide 200 to 1,600 µg/day vs triamcinolone 1,200 to 1,600 µg/day	OL, RCT Adult patients (≥18 years old) with persistent asthma enrolled in 25 United States health plans	N=945 52 weeks	Primary: Mean change from baseline to the end of treatment in symptom-free days Secondary: Changes from baseline in number of episode-free days, episode-free days at 52 weeks, FEV_1, FVC, asthma symptom scores, breakthrough bronchodilator use, HRQOL	Primary: Increase in mean estimated symptom- and episode-free days from baseline observed in both treatment groups by month 1 and were maintained throughout the treatment period. These increases were consistently greater with budesonide treatment than with triamcinolone treatment (7.74 and 5.73 for the budesonide group compared to 3.78 and 2.12 for the triamcinolone group; $P< 0.001$). Secondary: The adjusted mean increase in symptom- and episode-free days from baseline to month 12 and the estimated mean number of symptom- and episode-free days over the 52-week treatment period were significantly greater in the budesonide group than in the triamcinolone group ($P<0.001$). FEV_1 and FVC improved from baseline to week 52 in both treatment groups. Patients receiving budesonide treatment experienced a greater

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				improvement in FEV_1 than patients receiving triamcinolone (0.35 L vs 0.25 L; *P*=0.005). The difference between the 2 treatment groups in FVC was not statistically significant. Mean daytime and nighttime asthma symptom scores decreased from baseline in both groups. Decreases were significantly greater in patients receiving budesonide at month 12 (*P*=0.001 and *P*<0.001, respectively). The mean amount of breakthrough bronchodilator use decreased from 4.42 to 2.58 puffs/week in the budesonide group (95% CI, -2.17 to -1.58) and from 4.56 to 3.68 puffs/week in the triamcinolone group (95% CI, -1.36 to -0.52; *P*<0.001). Patients in both treatment groups reported significant improvements from baseline over the course of the study in overall quality of life and the individual domains of the HRQOL questionnaire. Compared with the triamcinolone group, the budesonide group reported significantly greater improvements in SF-36 general health scores at weeks 26 and 52 (*P*<0.05 and *P*=0.001, respectively).
Study #323/324[54] Ciclesonide 160 µg twice daily vs ciclesonide 320 µg twice daily vs fluticasone 440 µg twice daily vs	AC, DB, MC, PC, PG, RCT Patients ≥12 years old with a history of persistent asthma for ≥ 1 year prior to screening, a documented use of an ICS for the month prior to baseline, use of a β_2-agonist for more than 2 times a week for the month prior to	N=531 12 weeks	Primary: Change from baseline to week 12 in morning pre-dose FEV_1 compared to placebo Secondary: Change from baseline to week 12 in morning PEF, change from baseline to week 12 in albuterol utilization, change in asthma symptom score, change in AQLQ score, adverse events	Primary: All three treatment arms showed a statistically significant improvement in FEV_1 scores from baseline to week 12. Change for the 160 µg twice daily group, 0.11 L (*P*=0.0374). Change for the 320 µg twice daily group, 0.18 L (*P*=0.0008). Change for the fluticasone 440 µg twice daily group, 0.24 L (*P*=0.0001). Secondary: All treatment arms showed a statistically significant improvement compared to placebo in change from baseline to week 12 in morning PEF. Change for the 160 µg twice daily group, 27.8 L/min (*P*=0.0001). Change for the 320 µg twice daily group, 30.39 L/min (*P*=0.0001). Change for the fluticasone 440 µg twice daily group, 41.42 L/min (*P*=0.0001). All treatment arms showed a statistically significant improvement compared to placebo in change from baseline to week 12 in albuterol utilization (puffs/day). Change for the 160 µg twice daily group, -1.69

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo	screening with an FEV_1 of ≤80% of predicted normal following a 6 hour β_2-agonist treatment withholding period at screening and an FEV_1 between 40 to 50% of predicted normal following a 6 hour β_2-agonist treatment withholding period			(*P*=0.0001). Change for the 320 µg twice daily group, -1.57 (*P*=0.0001). Change for the fluticasone 440 µg twice daily group, -2.19 (*P*=0.0001). For total asthma symptom score (0 to 5 scale) the treatment difference was statistically significant for all three groups. Change for the 160 µg twice daily group, -0.71 (*P*=0.0001). Change for the 320 µg twice daily group, -0.80 (*P*=0.0001). Change for the fluticasone 440 µg twice daily group, -0.91 (*P*=0.0001). All four domains (exposure to environmental stimuli, symptoms, activity limitation, and emotional function) in the AQLQ were statistically significantly improved in all 3 treatment arms (*P* value not reported).The percentage of patients who achieved the MID (an increase of at least 0.5) in the AQLQ overall score at week 12 were: 42.5% in the 160 µg twice daily group, 43.1% in the 320 µg twice daily group, 58.8% in the 440 µg fluticasone twice daily group, and 26.9% in the placebo group. The percentage of patients who experienced treatment emergent adverse events was comparable among treatment groups (160 µg, 61.4%; 320 µg, 54.6%; 440 µg, 60.1%; placebo, 61.8%). The most common adverse event that occurred in at least 5% of patients for the treatment groups was nasopharyngitis. The incidence of oropharyngeal adverse events was more common in the fluticasone treatment arm than in the ciclesonide. Oral candidiasis occurred in 1.6%, 0%, 11.6%, 2.2%, pharyngitis in 4.7%, 3.1%, 5.1%, 2.9% and dysphonia in 0%, 1.5%, 3.6%, 0.7% all in the ciclesonide 160 µg twice daily, 320 µg twice daily, fluticasone 440 µg twice daily and placebo groups respectively.
Sheikh et al[55] Flunisolide 1,500 µg/day for a period of one year then crossed over to fluticasone 880 µg/day for one year	OL, XO Children with moderate to severe asthma, mean age of 12.7 years	N=30 2 years	Primary: Mean percent predicted values for FVC, FEV_1, $FEF_{25\%-75\%}$, and PEFR Secondary: Not reported	Primary: Significant improvement in all clinical parameters was found while patients were receiving fluticasone as compared with flunisolide. There was significant improvement in FVC during the 2 to 6 month and 7- to 12-month time periods after the switch. Significant improvement was noted in FEV_1 and $FEF_{25\%-75\%}$ at 1 month after the switch, and this improvement persisted during the 2 to 6 months

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				and 7 to 12 month time periods. There was no significant difference in PEFR at any time period. Secondary: Not reported
Nakanishi et al[56] Flunisolide with a valved holding chamber, four inhalations (1 mg) twice daily for 7 days and daily placebo tablets vs oral prednisone 2 mg/kg (maximum of 60 mg/day) for 7 days, and placebo pressurized MDI, four inhalations twice daily	PC, PG, RCT Children aged 6 to 16 years seeking emergent care for an acute exacerbation of asthma	N=58 7 days	Primary: Percentage of predicted FEV_1 Secondary: Symptom score, initial vital signs and oximetry, side effects, recurrence rate for acute asthma symptoms, and daily PEF	Primary: The FEV_1 percentage of predicted for the inhaled corticosteroids group was lower on day 3 (65% vs 78% for oral corticosteroids; *P*=0.03) and on day 7 (77% vs 95%; *P*=0.002). Both groups continued to improve over the 7-day study period, with the most improvement in those patients receiving oral corticosteroids. Secondary: There was no significant difference in symptom severity between the two groups at any time during the study. There was no significant difference in initial vital signs or oximetry between the two groups at any time during the study. One patient in the inhaled corticosteroid group required additional corticosteroids after the 7-day study period to control symptoms. One patient in the oral corticosteroid group required hospital admission for asthma within 24 hours following enrollment. There was no significant difference in PEF between the two groups at any time during the study.
Harnest et al[57] Fluticasone 500 µg twice daily vs mometasone 500 µg twice daily	AC, RCT Patients ≥18 years of age with moderate to severe persistent asthma who were previously using ICS for daily	N=203 12 weeks	Primary: Change from baseline in weekly average PEF Secondary: FEV_1, asthma symptom scores, rescue medication use, response to therapy,	Primary: The percent change from baseline in PEF was 7.8 for the mometasone group and 7.7 for the fluticasone group (*P*=0.815). Secondary: At week-12 the change from baseline in FEV_1 was 0.4 L in both the mometasone and fluticasone group (*P*=0.988). Morning and evening asthma symptom scores were not significantly

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	maintenance therapy for ≥30 days		adverse events	different between mometasone (-.05,-0.6; *P*=0.251) and fluticasone (-0.6, -0.7; *P*=0.251). Rescue albuterol use decreased from baseline in both treatment groups with no significant differences between groups (*P*=0.890). Treatment-emergent adverse events occurred in 51% of the patients in the mometasone group, and in 43% of the patients in the fluticasone group. The difference between the two groups was not significant (*P* value not reported).
O'Connor et al[58] Fluticasone 250 µg twice daily vs mometasone 100, 200, or 400 µg twice daily	DB, MC, PG, RCT Patients with moderate persistent asthma previously treated with ICS	N=733 12 weeks	Primary: Change in FEV_1 Secondary: Mean changes from baseline in PEFR, $FEF_{25\%-75\%}$, FVC, asthma symptom scores, albuterol use, nocturnal awakenings due to asthma, and physician-evaluation of response to therapy	Primary: At study endpoint, all treatment groups showed improvement in FEV_1. No statistical difference was observed between the mometasone 200 µg, 400 µg, or fluticasone group. The mometasone 400 µg twice daily group showed significant improvement in FEV_1 compared with the mometasone 100 µg twice daily group (*P*=0.02). Mometasone 200 µg twice daily and fluticasone groups showed similar improvements in FEV_1. Secondary: $FEF_{25\%-75\%}$ and PEFR were significantly improved in the mometasone 200 µg twice daily, 400 µg twice daily, and fluticasone groups compared with the mometasone 100 µg twice daily group. All other results showed no significant differences between the treatment groups.
Wardlaw et al[59] Fluticasone 250 µg twice daily vs mometasone 400 µg every evening	OL, PG, RCT Patients with moderate persistent asthma previously using fluticasone	N=167 8 weeks	Primary: Percent change in FEV_1 from baseline to endpoint Secondary: FVC, PEFR, asthma symptom scores, albuterol use, and	Primary: No significant difference in the percent change in FEV_1 (*P*≥0.14) was observed between treatment groups at any point in the study (2, 4, and 8 weeks of treatment). Secondary: No significant difference in the percent change in FVC (*P*≥0.24), PEFR (*P*=0.60), albuterol use or asthma symptom scores (*P*≥0.06) was observed between treatment groups at any point in the study (2, 4, and 8 weeks of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			device evaluation	treatment). There was a greater number of subjects that showed improvement in their asthma symptoms in the mometasone group compared with the fluticasone group (*P*=0.007) as reported by physicians' evaluations of response to therapy. A significantly greater number of subjects reported having "liked the inhaler a lot" in the mometasone group versus the fluticasone group (*P*=0.01).
Condemi et al[60] Fluticasone 250 µg twice daily vs triamcinolone 200 µg four times daily vs placebo twice daily or four times daily	DB, DD, PC, PG, RCT Male and female patients at least 12 years of age with asthma (FEV_1 between 50 to 80% of predicted value) who had previously received maintenance therapy with beclomethasone or triamcinolone	N=291 24 weeks	Primary: Morning predose FEV_1, probability of remaining in the study over time, patient-measured PEF, albuterol use, number of nighttime awakenings requiring albuterol, asthma symptom scores Secondary: Adverse events, morning plasma cortisol levels	Primary: At end point, patients in both the fluticasone and triamcinolone groups experienced statistically significant improvements in FEV_1 compared with the placebo group (-0.18 L for placebo, 0.07 for triamcinolone, 0.27 for fluticasone; $P \leq 0.001$). Only 27% of patients in the placebo group remained in the study over time compared with 66% in the fluticasone group and 55% in the triamcinolone group. Survival analysis suggested that patients in both active treatment groups had a significantly greater probability of remaining in the study over time than patients in the placebo group (*P*<0.001). There was no significant difference seen between the two active treatment groups. Significant differences in mean change in PEF between the triamcinolone and fluticasone groups were observed by week 1 and maintained throughout the treatment period (*P*<0.05). At end point, the mean increase over baseline values in patients who switched to fluticasone was 21 L/min compared with mean decreases of 6 L/min and 28 L/min in the triamcinolone and placebo groups, respectively (*P*<0.001). Patients treated with fluticasone had reduced albuterol use by 30% and those in the triamcinolone group by 6%. Patients in the placebo group increased their albuterol use by 50% (*P*<0.05). At end point, the number of nighttime awakenings requiring albuterol significantly decreased ($P \leq 0.001$ vs placebo) with either fluticasone (-0.03

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				SEM) or triamcinolone (-0.01 SEM). Nighttime awakenings increased after treatment with placebo (0.27 SEM; *P*<0.05). There were no significant differences between the treatment groups with respect to symptom scores. Secondary: 13% of patients in the placebo group, 15% of the fluticasone group, and 8% of the triamcinolone group experienced at least one adverse event that was considered to be potentially related to treatment during the study (sore throat, oral candidiasis, hoarseness). 1% of patients in the placebo group, 3% in the triamcinolone group, and 1% in the fluticasone group has morning plasma cortisol concentrations less than 5 µg/ml.
Berend et al[61] Fluticasone at approximately half the dose of their run-in ICS vs continuing the same dose of ICS used during the 4-week run-in period (beclomethasone or budesonide)	MC, OL, PG, RCT Patients aged 18 years or older, with a history of severe asthma who were currently receiving at least 1,750 µg /day or inhaled beclomethasone or budesonide	N=133 6 months	Primary: Changes in morning PEF, changes in FEV_1 at clinic visits Secondary: Changes in relevant laboratory values, adverse events, asthma exacerbations, QOL	Primary: At week 6, patients in the fluticasone group showed a significant improvement in morning PEF and this improvement was maintained until the end of the study (adjusted difference between two groups, 26±32 L/min; 95% CI, 8 to 45; *P*=0.006). Changes in FEV_1 measured at clinic visits paralleled those values of the morning PEF (fluticasone, 1.87±0.70 L; beclomethasone/budesonide 2.03±0.86 L; *P* value not reported). Secondary: Serum osteocalcin levels increased significantly only in the fluticasone group (adjusted mean [SD] = 2.6 [4.0] µg/L, 95% CI, 0.2 to 4.9; *P*=0.03). There were no clinically significant changes during the study in plasma creatinine, plasma glucose, serum insulin, serum fasting lipids, or in any parameter associated with the calcium-parathyroid axis or the renal handling of calcium. There was no significant difference in the analysis of change in hoarseness between the two treatment groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There was a low incidence of oropharyngeal candidiasis during the study in both treatment groups. By week 24, four patients (6%) in the fluticasone group and one patient (2%) in the beclomethasone/budesonide group had evidence of candidiasis. An analysis of change did not show any significant difference between the two groups. Thirty-four patients (51%) in the fluticasone group and 36 patients (55%) in the beclomethasone/budesonide group reported one or more exacerbations during the course of the trial. No significant difference seen in the incidence of asthma between the groups. There was a significant increase in the overall asthma quality of life score in the fluticasone group (4.8±1.1 to 5.5±1.1 units; *P*<0.001); no significant change was seen in the beclomethasone/budesonide group (4.9±1.1 to 5.0±1.2 units; *P*=0.13).
Chronic Obstructive Pulmonary Disease				
Weir et al[62] Beclomethasone 750 µg twice daily (<50 kg) or 1,000 µg twice daily (>50kg) vs placebo	DB, PC, PG, RCT Patients with COPD	N=98 24 months	Primary: Change in FEV_1, number of exacerbations Secondary: Change in histamine reactivity, respiratory symptoms	Primary: Decline in FEV_1 was less in the beclomethasone treated group although the difference did not reach statistical significance (mean FEV_1 decline, placebo 45.2 mL/year; budesonide 12.1 mL/year; 95% CI, -80 to 8 mL/year). The actively treated group had fewer exacerbations per year although the difference was not statistically significant (mean exacerbation rates per year: placebo 0.57, budesonide 0.36). Secondary: Bronchial reactivity to inhaled histamine showed no significant change in either active or placebo groups (placebo -0.09, budesonide -0.13). There was no significant effect of active treatment on the Mahler dyspnea index over the study period (placebo 5.4, beclomethasone 6.7; *P* value not reported).
Bourbeau et al[63] Budesonide 400 µg twice	DB, PC, PG, RCT Patients with	N=79 6 months	Primary: Decline in FEV_1	Primary: There was no difference in the change in FEV_1 from baseline between the treatment and placebo groups (-4 units difference; -95 to 87).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
daily via DPI vs placebo	COPD aged 40 years or older who did not respond to oral corticosteroids		Secondary: Exercise capacity, dyspnea with exertion, quality of life, PEFR, respiratory symptom scores	Secondary: None of the secondary endpoints differed significantly between the two groups: (treatment difference: budesonide vs placebo). Exercise capacity as measured by the 6-minute walking test, -28 units difference; -45 to -10. Dyspnea with exertion, 0.1 units difference; -1.0 to 1.1. QOL, 1.3 units difference; -4.1 to 1.5. Morning PEFR increased more from baseline in the budesonide group than in the placebo group, but this was observed after only four weeks of treatment and the difference was no longer apparent after one month of treatment. Symptom scores with budesonide did not produce a significant improvement compared with placebo.
Pauwels et al[64] Budesonide 400 µg twice daily via DPI vs placebo	DB, MC, PC, PG, RCT Current smokers aged 30 to 65 years with COPD	N=1,277 36 months	Primary: Change in FEV_1 Secondary: Adverse events	Primary: In the 912 patients who completed the study, the median decline in FEV_1 over the three-year period was 140 mL in the budesonide group and 180 ml in the placebo group (P=0.05), or 4.3% and 5.3% of their respective predicted values (P=0.04). Secondary: More subjects in the budesonide group had skin bruising (10%) than the placebo group (4%; P<0.001). Serious adverse events were equally distributed between the groups. Seventy patients were withdrawn from the study in the budesonide group as compared with 62 in the placebo group (P=0.51).
Vestbo et al[65] Budesonide 800 µg in the morning and 400 µg in the evening daily for six	DB, PC, PG, RCT Patients with COPD	N=290 36 months	Primary: Rate of FEV_1 decline Secondary: Decrease in symptoms	Primary: No significant effect of budesonide was found on the rate of FEV_1 decline. The crude rate of loss of lung function was 41.8 mL per year in the placebo group and 45.1 mL per year in the budesonide group. The difference in estimated rates of decline (3.1 mL per year [95% CI, -12.8 to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
months followed by 400 µg twice daily for 30 months administered via DPI vs placebo for 36 months				19.0]) was not significant (*P*=0.70). Secondary: In both treatment groups, symptoms decreased substantially during the study period but no differences between the two groups was observed.
Burge et al[66] Fluticasone 500 µg twice daily vs placebo	DB, PC, RCT Patients with COPD with a mean FEV_1 50% of predicted normal	N=751 36 months	Primary: Rate of decline in FEV_1 Secondary: Frequency of exacerbations, changes in health status, withdrawals due to respiratory disease, morning serum cortisol levels, adverse events	Primary: The annual rate of decline in FEV_1 was 59 mL per year in the placebo group and 50 mL per year in the fluticasone group (*P*=0.16). The predicted mean FEV_1 at three and 36 months in the fluticasone group was 76 mL and 100 mL higher, respectively, than in the placebo group (*P*<0.001). Secondary: The median yearly exacerbation rate was lower in the fluticasone group (0.99 per year) compared with the placebo group (1.32 per year), a reduction of 25% in those receiving fluticasone (*P*=0.026). The respiratory health questionnaire score increased (i.e., health status declined) after the first six months of treatment and this increase was linear (*P*<0.001). The respiratory score worsened at a faster rate in the placebo group (3.2 units per year) than in the fluticasone group (2.0 units per year) (*P*=0.004). More patients in the placebo group than in the fluticasone group withdrew because of respiratory disease (25% vs 19%, respectively; *P*=0.034). There was a small decrease in mean cortisol concentrations with fluticasone compared with placebo (*P*≤0.032). No decreases were associated with any signs or symptoms of hypoadrenalism or other clinical effects. Reported events were similar between treatments overall, with the exception of side effects secondary to inhaled glucocorticoids: hoarseness (35 vs 16), throat irritation (43 vs 27), and candidiasis of the mouth and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				throat (41 vs 24) were more common in the fluticasone group than with placebo.
Paggiaro et al[67] Fluticasone 500 µg twice daily vs placebo	DB, PC, RCT Patients with COPD aged between 50 and 75 years	N=281 6 months	Primary: Number of patients who had at least one exacerbation at the end of the study period Secondary: Mean change from baseline in PEFR, daily symptom scores, frequency of adverse events	Primary: More patients in the placebo group (37%) experienced at least one exacerbation than in the fluticasone group (32%) (*P*<0.001). Secondary: The adjusted mean change from baseline daily PEFR in the placebo group was -2 L/min compared with 15 L/min in the fluticasone group (9-26; *P*<0.001). Symptom scores showed a distribution of significantly lower median daily cough scores in the fluticasone group compared with the placebo group (*P*=0.004). The overall frequency of adverse events during treatment was similar in the two treatment groups, occurring in 68% of patients receiving placebo and 64% of patients receiving fluticasone.
Lung Health Study Research Group[68] Triamcinolone 600 µg twice daily vs placebo	PC, RCT Patients with COPD with FEV_1 30 to 90% of predicted value	N=1,116 48 months	Primary: Rate of decline in FEV_1 Secondary: Respiratory symptoms, use of health care services, airway reactivity	Primary: There were no significant effects of treatment assignment on the decline in FEV_1. The mean decline in FEV_1 in the triamcinolone group was 44.2$\pm$2.9 mL per year, as compared with 47.0$\pm$3.0 mL per year in the placebo group (95% CI, -11 to 5.4 mL per year for the difference). Secondary: The incidence of respiratory symptoms did not differ significantly between the treatment groups, with the exception of dyspnea, which was more frequent in the placebo group (*P*=0.02). Unscheduled physicians' visits and hospitalizations for respiratory conditions were less frequent in the triamcinolone group (*P*<0.07). At 9 and 33 months, the triamcinolone group had less reactivity in response to methacholine than the placebo group (*P*=0.02).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Lee et al[69] Exposure to ICSs, ipratropium, LABAs, theophylline, and SABAs	Nested case-control Patients treated in the United States Veterans Health Administration health care system	N=145,020 Cohort identified between October 1, 1999 and September 30, 2003 and followed through September 30, 2004	Primary: All-cause mortality, respiratory mortality, cardiovascular mortality Secondary: Subgroup analyses of primary outcomes	Primary: After adjusted for differences in covariates, ICSs and LABAs were associated with reduced odds of death. An adjusted OR of 0.80 (95% CI, 0.78 to 0.83) for ICSs and 0.92 (95% CI, 0.88 to 0.96) for LABAs was observed. Ipratropium was associated with an increased risk of death (OR, 1.11; 95% CI, 1.08 to 1.15). Theophylline exposure was associated with a statistically significant increase in respiratory deaths compared with the unexposed group (OR, 1.12; 95% CI, 1.46 to 2.00). An increase in the odds of respiratory death was observed with LABAs (OR, 1.12; 95% CI, 0.97 to 1.30), however the increase did not reach statistical significance. In addition, a decrease in the odds of respiratory death was observed with ICSs (OR, 0.88; 95% CI, 0.79 to 1.00), however this also did not reach statistical significance. Exposure to ipratropium was associated with a 34% increase in the odds of cardiovascular death (OR, 1.34; 95% CI, 0.97 to 1.47), whereas ICS exposure was associated with a 20% decrease (OR, 0.80; 95% CI, 0.72 to 0.88). LABAs (OR, 0.97; 95% CI, 0.99 to 1.37) and theophylline (OR, 1.16; 95% CI, 0.99 to 1.37) were not associated with statistically significant risks in cardiovascular deaths. Secondary: In a sensitivity analysis based on dose of medication, higher doses were associated with a larger effect than lower doses, consistent with a dose response to the medication. With current smoking associated with a RR for death of 1.5, these estimates would result in adjusted risk ratios of 0.77 for ICSs, 1.08 for ipratropium, and 0.90 for LABAs. Among the medication regimens, those that included theophylline were associated with increased risk for respiratory death. For cardiovascular death, ipratropium alone (OR, 1.42; 95% CI, 1.27 to 1.59) and ipratropium plus theophylline (OR, 1.47; 95% CI, 1.09 to 1.98) were associated with increased risk, whereas the presence of ICSs with ipratropium reduced the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				risk for cardiovascular death (OR, 1.04; 95% CI, 0.90 to 1.22; *P*<0.001). In the all-cause mortality group, ICS were consistently associated with reduced odds of death when used alone or in combination with other medications, whereas ipratropium and ipratropium plus theophylline were associated with elevated risk for death.

Study abbreviations: AC=active control, ANOVA= analysis of variance, CI=confidence interval, DB=double-blind, DD=double-dummy, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, XO=crossover, SEM=standard error of the mean
Miscellaneous abbreviations: AQLQ=asthma quality of life questionnaire, CFC=chlorofluorocarbon, COPD=chronic obstructive pulmonary disease, DPI=dry-powder inhaler, $FEF_{25-75\%}$=forced expiratory flow at 25-75% of FVC, FEV_1=forced expiratory volume in 1 second, FVC=forced vital capacity HFA=hydrofluoroalkane, HPA=hypothalamic-pituitary-adrenal, HRQOL= health-related quality of life, ICS=inhaled corticosteroid, LABA=long acting β_2-agonist, MDI = metered-dose inhaler, MID=minimally important difference, PACQLQ=Pediatric Asthma Caregiver's Quality of Life Questionnaire, PAQLQS=Pediatric Asthma Quality of Life Questionnaire, PEF=peak expiratory flow, PEFR=peak expiratory flow rate, QOL=quality of life, SABA=short acting β_2-agonist, SF-36= Short-Form-36, WMD=weighted mean difference

Special Populations

Table 5. Special Populations[1-11]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Beclomethasone	No dose adjustment is required in the elderly population. Dose adjustment is required in the pediatric population. Approved for use in children ages 5 and older.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Yes
Budesonide	No dose adjustment is required in the elderly population. Dose adjustment for the budesonide Flexhaler is required in the pediatric population. Budesonide Flexhaler approved for use in children ages 6 and older. Budesonide Respules approved for use in children ages 12 months to 8 years old.	Not studied in renal dysfunction.	No dosage adjustment required.	B	Yes (0.3% - 1%)
Ciclesonide	No dose adjustment is required in the elderly population. Dose adjustment is not required in the pediatric population. Approved for use in children ages 12 and older.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Yes
Flunisolide	No dose adjustment is required in the elderly population. Dose adjustment is required in the pediatric population.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Yes

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	Aerospan is approved for use in children ages 6 and older.				
Fluticasone	No dose adjustment is required in the elderly population. Dose adjustment is required in the pediatric population. Fluticasone Diskus and HFA are approved for use in children ages 4 and older.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Yes
Mometasone	No dose adjustment is required in the elderly population. Dose adjustment is required in the pediatric population. Approved for use in children ages 4 and older.	Not studied in renal dysfunction.	No dosage adjustment required.	C	Yes (<1%)
Triamcinolone	No dose adjustment is required in the elderly population. Dose adjustment is required in the pediatric population.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Yes

HFA=hydrofluoroalkane.

Adverse Drug Events

The most common adverse events associated with the inhaled corticosteroids as a class include oral candidiasis, cough at the time of inhalation, dysphonia, and headache.[15]

Table 6. Adverse Drug Events (%)[1-11,22]

Adverse Event(s)	Beclomethasone	Budesonide powder	Budesonide suspension	Ciclesonide	Flunisolide	Fluticasone	Mometasone	Triamcinolone
Cardiovascular								
Chest pain	-	-	1-3	-	3-9	1-3	-	-
Palpitations	-	-	-	-	3-9	-	-	-
Central Nervous System								
Dizziness	-	-	-	-	3-9	1-3	-	-
Headache	12-15	13-14	-	5-11	25	5-11	17-22	7-21
Nervousness	-	-	-	-	3-9	-	-	-
Dermatological								
Eczema	-	-	1-3	-	3-9	-	-	-
Pruritis	-	-	1-3	-	3-9	✔	-	-
Rash	-	-	1-4	-	3-9	-	-	1-3
Endocrine and Metabolic								
Edema	-	-	-	-	3-9	✔	-	1-3
Gastrointestinal								
Anorexia	-	-	1-3	-	3-9	-	1-3	-
Diarrhea	-	-	2-4	-	10	1-3	-	1-3
Dyspepsia	-	1-4	-	-	3-9	1-3	3-5	-
Gastroenteritis	-	1-3	4-5	-	-	-	1-3	-
Gastrointestinal pain	-	1-3	2-3	-	3-9	1-3	2-3	1-3
Oral candidiasis	-	2-4	-	-	3-9	2-5	4-6	-
Taste alteration	-	1-3	-	-	10	-	-	-
Vomiting	-	-	2-4	-	25	-	1-3	1-3
Respiratory								
Bronchitis	-	-	-	-	1-3	2-6	-	-
Cold symptoms	-	-	-	-	15	-	-	-
Coughing	1-3	-	5-8	-	3-9	4-6	-	-
Hoarseness	-	-	-	-	3-9	2-6	-	-
Increased asthma symptoms	3-8	-	-	-	-	✔	-	-
Nasal congestion	-	-	-	1.8-5.5	15	-	-	-
Pharyngitis	8-10	5-10	-	7-10.5	1-3	1-3	11-13	7-25
Rhinitis	6-11	-	7-12	3.1-5.5	3-9	1-3	11-15	-

Adverse Event(s)	Beclomethasone	Budesonide powder	Budesonide suspension	Ciclesonide	Flunisolide	Fluticasone	Mometasone	Triamcinolone
Sinusitis	-	2-11	-	-	-	4-7	-	2-9
Upper respiratory tract infection	9-12	19-24	34-38	4.1-8.7	25	16-18	8-15	-
Other								
Back pain	1-4	2-6	-	-	-	-	3-6	2-4
Dysmenorrhea	1-3	-	-	-	3-9	-	4-9	-
Dysphonia	2-4	1-6	1-3	-	-	-	1-3	1-3
Ear infection	-	-	2-5	-	3-9	-	-	-
Fever	-	2-4	-	-	3-9	1-3	-	-
Flu syndrome	-	6-14	1-3	-	10	-	-	2-4
Otitis media	-	-	9-12	-	-	-	-	-
Pain	2-3	5	-	-	-	1-3	1-3	1-3
Sore Throat	-	-	-	-	20	8-10	-	-
Viral infection	-	-	3-5	-	-	-	-	-

-Event not reported or incidence <1%.

Contraindications/Precautions[1-11]

All inhaled corticosteroids (ICS) are contraindicated for the primary treatment of status asthmaticus or in any other acute asthma episodes where intensive measures might be required. These agents are additionally contraindicated in patients with hypersensitivity to any of the ingredients that are included in the products.

A precaution of note is that the systemic absorption of ICS can potentially lead to suppression of the hypothalamic-pituitary-adrenal (HPA) axis. Particular attention should be placed on monitoring for the occurrence of adrenal suppression effects. If these effects do occur the patient's ICS dose should be decreased in accordance with acceptable procedures. Additionally, when transferring patients from oral systemic corticosteroids to any ICS, particular care is required as deaths due to adrenal insufficiency have occurred, as have the exacerbation of conditions previously controlled by systemic therapy, such as arthritis, rhinitis, eczema, etc.

Patients being treated with these agents have also, in rare cases, presented with systemic eosinophilia. Clinical features of the eosinophilia, such as vasculitis, can be consistent with Churg-Strauss syndrome. Health care providers should be alert to the presentation of eosinophilia, vasculitic rash, worsening of pulmonary symptoms, cardiac complications, and neuropathy in patients.

Bronchospasms or an immediate increase in wheezing may occur after dosing with any ICS agent. If bronchospasm do occur they should be treated with a fast-acting inhaled bronchodilator.

Patients who are being treated with these medications for prolonged periods have an increased risk of secondary infections due to immunosuppression. Viral infections such as chickenpox or measles can have a much more serious course in the susceptible adult or pediatric population. Particular care should be taken to avoid exposure in patients who have not had either of these diseases or have not been properly immunized. Furthermore these combination agents should be used with caution in patients with active or quiescent tuberculosis infection, untreated systemic fungal infections, bacterial, viral, or parasitic infections, or ocular herpes simplex.

In the pediatric population, ICS can cause a decrease in growth velocity. Pediatric patients who are receiving ICS routinely should have their growth monitored.

The use of long-term ICS also leads to the development of oropharyngeal fungal infections. Patients should be advised to rinse their mouth after inhalation of either agent. A decrease in bone mineral density has also been observed with long term ICS treatment. Patients with major risk factors for decreased mineral content should be monitored and treated with the established standards of care. Close monitoring of patients with glaucoma and cataracts who are being treated with ICS is also recommended as increased intraocular pressure has been observed. Routine ocular examination should be considered in this patient population.

Drug Interactions

Table 7. Drug Interactions[22]

Generic Name	Interacting Medication or Disease	Potential Result
Inhaled corticosteroids	CYP3A4 (i.e. azole antifungals, protease inhibitors)	CYP3A4 inhibitors such as the azole antifungals (ketoconazole, fluconazole) may inhibit the metabolism of corticosteroids resulting in enhanced corticosteroid effects and toxicity. Doses of inhaled corticosteroids may need to be adjusted.

Dosage and Administration

Table 8. Dosing and Administration[1-11]

Generic Name	Adult Dose	Pediatric Dose	Availability§
Beclomethasone	Asthma: HFA MDI: Patients treated previously with only bronchodilators, initial, 40 to 80 µg twice daily; maximum, 320 µg twice daily HFA MDI: Patients treated previously with an inhaled corticosteroid, initial, 40 to 160 µg twice daily; maximum, 320 µg twice daily	Asthma: HFA MDI: Children 5 to 11 years of age treated previously with only bronchodilators or with inhaled corticosteroids, initial, 40 µg twice daily; maximum, 80 µg twice daily	HFA MDI (100 inhalations): 40 µg 80 µg
Budesonide	Asthma: DPI: initial, 360 µg twice daily (selected patients can be initiated at 180 µg twice daily); maximum, 720 µg twice daily	Asthma: DPI: Children 6 to 17 years of age, initial, 180 µg twice daily (selected patients can be initiated at 360 µg twice daily); maximum, 360 µg twice daily Inhalation suspension: Children 12 months to 8 years of age treated previously with only bronchodilators, initial, 0.5 mg total daily dose administered either once or twice daily in divided doses; maximum, 0.5 mg total daily dose Inhalation suspension: Children 12 months to 8 years of age treated previously with an inhaled corticosteroid, initial, 0.5 mg total daily dose administered either once or twice daily in divided doses; maximum, 1 mg total daily dose Inhalation suspension: Children 12 months to 8 years of age treated previously with an oral corticosteroid, initial, 1 mg total daily dose administered either as 0.5 mg twice daily or 1 mg once daily; maximum, 1 mg total daily dose	DPI (Flexhaler™)(60 and 120 inhalations): 90 µg 180 µg Inhalation suspension (Respules®) (Each carton contains 30 Respules; each Respule is 2 mL): 0.25 mg/2 mL 0.5 mg/2 mL 1 mg/2 mL

Generic Name	Adult Dose	Pediatric Dose	Availability[§]
Ciclesonide	Asthma: HFA MDI: Patients treated previously with only bronchodilators, initial, 80 µg twice daily; maximum, 160 µg twice daily HFA MDI: Patients treated previously with an inhaled corticosteroid, initial, 80 µg twice daily; maximum, 320 µg twice daily HFA MDI: Patients treated previously with oral corticosteroids, initial, 320 µg twice daily; maximum, 320 µg twice daily	Asthma: HFA MDI: Children 12 years of age and older treated previously with only bronchodilators, initial, 80 µg twice daily; maximum, 160 µg twice daily HFA MDI: Children 12 years of age and older treated previously with an inhaled corticosteroid, initial, 80 µg twice daily; maximum, 320 µg twice daily HFA MDI: Children 12 years of age and older treated previously with oral corticosteroid, initial, 320 µg twice daily; maximum, 320 µg twice daily	HFA MDI (60 inhalations): 80 µg 160 µg
Flunisolide	Asthma: HFA MDI: initial, 160 µg twice daily; maximum, 320 µg twice daily CFC MDI: initial, 500 µg twice daily; maximum, 1,000 µg twice daily	Asthma: HFA MDI: Children 6 to 11 years of age, initial, 80 µg twice daily; maximum, 160 µg twice daily CFC MDI: Children 6 to 15 years of age, 500 µg twice daily; maximum 500 µg twice daily	HFA MDI (60 and 120 inhalations): 80 µg CFC MDI (100 inhalations): 250 µg
Fluticasone	Asthma: DPI: Patients treated previously with only bronchodilators, initial, 100 µg twice daily; maximum, 500 µg twice daily DPI: Patients treated previously with an inhaled corticosteroid, initial, 100 to 250 µg twice daily; maximum, 500 µg twice daily DPI: Patients treated previously with oral corticosteroids, initial, 500 to 1,000 µg twice daily; maximum, 1,000 µg twice daily HFA MDI: Patients treated previously with only bronchodilators, initial, 88 µg twice daily; maximum, 440 µg twice daily	Asthma: DPI: Children 4 to 11 years of age treated previously with only bronchodilators or with inhaled corticosteroids, initial, 50 µg twice daily; maximum, 100 µg twice daily HFA MDI: Children 4 to 11 years of age, initial 88 µg twice daily, maximum 88 µg twice daily	DPI (Diskus™) (60 inhalations): 50 µg 100 µg 250 µg HFA MDI (120 inhalations): 44 µg 110 µg 220 µg

Generic Name	Adult Dose	Pediatric Dose	Availability[§]
	HFA MDI: Patients treated previously with an inhaled corticosteroid, initial, 88 to 220 µg twice daily; maximum, 440 µg twice daily HFA MDI: Patients treated previously with oral corticosteroids, initial, 440 µg twice daily; maximum, 880 µg twice daily		
Mometasone	Asthma: DPI: Patients treated previously with only bronchodilators or inhaled corticosteroids, initial, 220 µg once daily in the evening; maximum, 440 µg administered as once daily in the evening or as 220 µg twice daily DPI: Patients treated previously with oral corticosteroids, initial, 440 µg twice daily; maximum, 880 µg daily	Asthma: DPI: Children 4 to 11 years of age, initial, 110 µg once daily in the evening; maximum, 110 µg once daily in the evening	DPI (Twisthaler®) (14, 30, 60 and 120 inhalations): 110 µg 220 µg
Triamcinolone	Asthma: CFC MDI: initial, 150 µg three to four times daily or 300 µg twice daily; maximum, 1,200 µg daily	Asthma: CFC MDI: Children 6 to 12 years of age, initial, 75 to 150 µg three to four times daily or 150 to 300 µg twice daily; maximum, 900 µg daily	CFC MDI (240 inhalations): 75 µg

CFC=chlorofluorocarbons, DPI=dry powder inhaler, HFA=hydrofluoroalkane, MDI=meter dose inhaler.
[§] Some inhalation amounts are specific to certain strengths.

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guidelines	Recommendations
The National Heart, Lung, and Blood Institute (NHLBI)/ National Asthma Education and Prevention Program (NAEPP): **Guidelines for the Diagnosis and Management of Asthma (2007)**[17]	Diagnosis • To establish a diagnosis of asthma, a clinician must determine the presence of episodic symptoms or airflow obstruction, partially reversible airflow obstruction, and alternate diagnoses must be excluded. • The recommended methods to establish a diagnosis are a detailed medical history, physical exam focusing on the upper respiratory tract, spirometry to demonstrate obstruction and assess reversibility, and additional studies to exclude alternate diagnoses. • A diagnosis of asthma should be considered if any of the following indicators are present: wheezing, history of cough, recurrent wheeze, difficulty breathing or chest tightness, symptoms that occur or worsen with exercise or viral infections, and symptoms that occur or worsen at night. • Spirometry is needed to establish a diagnosis of asthma. • Additional studies such as additional pulmonary function tests, bronchoprovocation, chest x-ray, allergy testing, and biomarkers of

Clinical Guidelines	Recommendations
	inflammation may be useful when considering alternative diagnoses. Treatment • Pharmacologic therapy is used to prevent and control asthma symptoms, improve quality of life, reduce the frequency and severity of asthma exacerbations, and reverse airflow obstruction. • For initiating treatment, asthma severity should be classified, and the initial treatment should correspond to the appropriate severity category. • Long-term control medications such as inhaled corticosteroids (ICSs), long-acting bronchodilators, leukotriene modifiers, cromolyn, theophylline, and immunomodulators should be taken daily on a long-term basis to achieve and maintain control of persistent asthma. • Quick-relief medications are used to provide prompt relief of bronchoconstriction and accompanying acute symptoms such as cough, chest tightness, and wheezing. • Quick relief medications include short-acting β_2-agonists (SABAs), anticholinergics, and systemic corticosteroids. Long-term Control Medications • ICSs are the most potent and consistently effective long-term control medication for asthma in patients of all ages. • Short courses of oral systemic corticosteroids may be used to gain prompt control when initiating long-term therapy and chronic administration is only used for the most severe, difficult-to-control asthma. • When patients ≥12 years of age require more than low-dose ICSs, the addition of a long-acting β_2-agonist (LABA) is recommended. Alternative, but not preferred, adjunctive therapies include leukotriene receptor antagonists (LTRAs), theophylline, or in adults, zileuton. • Mast cell stabilizers (cromolyn and nedocromil) are used as alternatives for the treatment of mild persistent asthma. They can also be used as preventative treatment prior to exercise or unavoidable exposure to known allergens. • Omalizumab, an immunomodulator, is used as adjunctive therapy in patients ≥12 years old who have allergies and severe persistent asthma that is not adequately controlled with the combination of high-dose ICS and LABA therapy. • LTRAs (montelukast and zafirlukast) are alternative therapies for the treatment of mild persistent asthma. • LABAs (salmeterol and formoterol) are not to be used as monotherapy for long-term control of persistent asthma. • LABAs should continue to be considered for adjunctive therapy in patients ≥5 years of age who have asthma that require more than low-dose ICSs. For patients inadequately controlled on low-dose ICSs, the option to increase the ICS should be given equal weight to the addition of a LABA. • Methylxanthines, such as sustained-release theophylline, may be used as an alternative treatment for mild persistent asthma. • Tiotropium bromide is a long-acting inhaled anticholinergic indicated once-daily for chronic obstructive pulmonary disease and has not been studied in the long-term management of asthma. Quick-relief Medications • SABAs are the therapy of choice for relief of acute symptoms and prevention of exercise induced bronchospasm.

<table>
<tr><th>Clinical Guidelines</th><th>Recommendations</th></tr>
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There is inconsistent data regarding the superior efficacy of levalbuterol over albuterol. Some studies suggest an improved efficacy while other studies fail to detect any advantage of levalbuterol.
Anticholinergics may be used as an alternative bronchodilator for patients who do not tolerate SABAs and provide additive benefit to SABAs in moderate-to-severe asthma exacerbations.
Systemic corticosteroids are used for moderate and severe exacerbations as adjunct to SABAs to speed recovery and prevent recurrence of exacerbations.
The use of LABAs is not currently recommended to treat acute symptoms or exacerbations of asthma.

<u>Assessment, Treatment, and Monitoring</u>

A stepwise approach to managing asthma is recommended to gain and maintain control of asthma in both the impairment and risk domains.
Regularly scheduled, daily, chronic use of a SABA is not recommended. Increased use or SABA use >2 days a week for symptom relief generally indicates inadequate asthma control.
The stepwise approach for managing asthma is outlined below:

<table>
<tr><th>Inter-mittent Asthma</th><th colspan="5">Persistent Asthma: Daily Medication</th></tr>
<tr><th>Step 1</th><th>Step 2</th><th>Step 3</th><th>Step 4</th><th>Step 5</th><th>Step 6</th></tr>
<tr><td><u>Preferred</u>
SABA as needed</td><td><u>Preferred</u>
Low-dose ICS

<u>Alternative</u>
Cromolyn, LTRA, nedocromil, or theophylline</td><td><u>Preferred</u>
Low-dose ICS+LABA OR medium-dose ICS

<u>Alternative</u>
Low-dose ICS+either a LTRA, theophylline, or zileuton</td><td><u>Preferred</u>
Medium-dose ICS+LABA

<u>Alternative</u>
Medium-dose ICS+either a LTRA, theophylline, or zileuton</td><td><u>Preferred</u>
High-dose ICS+LABA AND consider omalizumab for patients who have allergies</td><td><u>Preferred</u>
High-dose ICS+LABA+ oral steroid AND consider omalizumab for patients who have allergies</td></tr>
</table>
<u>Management of Exacerbations</u>

Appropriate intensification of therapy by increasing inhaled SABAs and, in some cases, adding a short course of oral systemic corticosteroids is recommended.

<u>Special Populations</u>

For exercise induced bronchospasm, pretreatment before exercise with either a SABA or LABA is recommended. LTRAs may also attenuate exercise induced bronchospasm and mast cell stabilizers can be taken shortly before exercise as an alternative treatment for prevention however they are not as effective as SABAs. The addition of cromolyn to a SABA is helpful in some individuals who have exercise induced bronchospasm.
Consideration of the risk for specific complications must be given to patients who have asthma who are undergoing surgery.
Albuterol is the preferred SABA in pregnancy because of an excellent safety profile.
ICSs are the preferred treatment for long-term control medication in pregnancy. Specifically, budesonide is the preferred ICS as more data is available on using budesonide in pregnant women than other ICSs.

</td></tr>
</table>

Clinical Guidelines	Recommendations
Global Initiative for Asthma (GINA): **Global Strategy for Asthma Management and Prevention (2008)**[18]	Diagnosis • A clinical diagnosis of asthma is often prompted by symptoms such as episodic breathlessness, wheezing, cough, and chest tightness. • Measurements of lung function (spirometry or peak expiratory flow) provide an assessment of the severity of airflow limitation, its reversibility, and its variability and provide confirmation of the diagnosis of asthma. Treatment • Education should be an integral part of all interactions between health care professionals and patients, and is relevant to asthma patients of all ages. • Measures to prevent the development of asthma, asthma symptoms, and asthma exacerbations by avoiding or reducing exposure to risk factors should be implemented whenever possible. • Controller medications are administered daily on a long-term basis and include inhaled and systemic glucocorticosteroids, leukotriene modifiers, LABAs in combination with inhaled glucocorticosteroids, sustained-released theophylline, cromones, and anti-immunoglobulin E (IgE). • Reliever medications are administered on an as-needed basis to reverse bronchoconstriction and relieve symptoms and include rapid-acting inhaled β_2-agonists, inhaled anticholinergics, short-acting theophylline, and SABAs. Controller Medications • Inhaled glucocorticosteroids are currently the most effective anti-inflammatory medications for the treatment of persistent asthma for patients of all ages. • Inhaled glucocorticosteroids differ in potency and bioavailability, but few studies have been able to confirm the clinical relevance of these differences. • To reach clinical control, add-on therapy with another class of controller is preferred over increasing the dose of inhaled glucocorticosteroids. • Leukotriene modifiers are generally less effective than inhaled glucocorticosteroids therefore may be used as an alternative treatment in patients with mild persistent asthma. • Some patients with aspirin-sensitive asthma respond well to leukotriene modifiers. • Leukotriene modifiers used as add-on therapy may reduce the dose of inhaled glucocorticosteroids required by patients with moderate to severe asthma, and may improve asthma control in adult patients whose asthma is not controlled with low or high doses of inhaled glucocorticosteroids. • Several studies have demonstrated that leukotriene modifiers are less effective than LABAs as add-on therapy. • LABAs should not be used as monotherapy in patients with asthma as these medications do not appear to influence asthma airway inflammation. • When a medium dose of an inhaled glucocorticosteroid fails to achieve control, the addition of a LABA is the preferred treatment. • Controlled studies have shown that delivering a LABA and an inhaled glucocorticosteroid in a combination inhaler is as effective as giving each drug separately. Fixed combination inhalers are more convenient, may increase compliance, and ensure that the LABA is always accompanied by a glucocorticosteroid. • Although the guideline indicates that combination inhalers containing formoterol and budesonide may be used for both rescue and maintenance,

Clinical Guidelines	Recommendations
	this use is not approved by the Food and Drug Administration (FDA). • Theophylline as add-on therapy is less effective than LABAs but may provide benefit in patients who do not achieve control on inhaled glucocorticosteroids alone. • Cromolyn and nedocromil are less effective than a low dose of an inhaled glucocorticosteroid. • Oral LABA therapy is used only on rare occasions when additional bronchodilation is needed. • Anti-IgE treatment with omalizumab is limited to patients with elevated serum levels of IgE. • Long-term oral glucocorticosteroid therapy may be required for severely uncontrolled asthma, but is limited by the risk of significant adverse effects. • Other anti-allergic compounds have limited effect in the management of asthma. <u>Reliever Medications</u> • Rapid-acting inhaled β_2-agonists are the medications of choice for the relief of bronchospasm during acute exacerbations and for the pretreatment of exercise-induced bronchoconstriction, in patients of all ages. • Rapid-acting inhaled β_2-agonists should be used only on an as-needed basis at the lowest dose and frequency required. • Although the guidelines states that formoterol, a LABA, is approved for symptom relief because of its rapid onset of action, and that it should only be used for this purpose in patients on regular controller therapy with inhaled glucocorticosteroids, the use of this agent as a rescue inhaler is not approved by the FDA. • Ipratropium bromide, an inhaled anticholinergic, is a less effective reliever medication in asthma than rapid-acting inhaled β_2-agonists. • Short-acting theophylline may be considered for relief of asthma symptoms. • Short-acting oral β_2-agonists (tablets, solution, etc.) are appropriate for use in patients who are unable to use inhaled medication however they are associated with a higher prevalence of adverse effects. • Systemic glucocorticosteroids are important in the treatment of severe acute exacerbations. <u>Assessment, Treatment, and Monitoring</u> • The goal of asthma treatment is to achieve and maintain clinical control. • To aid in clinical management, a classification of asthma by level of control is recommended: controlled, partly controlled, or uncontrolled. • Treatment should be adjusted in a continuous cycle driven by the patient's asthma control status and treatment should be stepped up until control is achieved. When control is maintained for at least three months, treatment can be stepped down. • Increased use, especially daily use, of reliever medication is a warning of deterioration of asthma control and indicates the need to reassess treatment.

<table>
<tr><th>Clinical Guidelines</th><th>Recommendations</th></tr>
<tr><td></td><td>
• The management approach based on control is outlined below:
<table>
<tr><th>Step 1</th><th>Step 2</th><th>Step 3</th><th>Step 4</th><th>Step 5</th></tr>
<tr><td colspan="5">Asthma education and environmental control</td></tr>
<tr><td colspan="5">As needed rapid-acting β_2-agonist</td></tr>
<tr><td rowspan="5">Controller options</td><td>Select one</td><td colspan="2">Select one</td><td>Add one or more</td><td>Add one or both</td></tr>
<tr><td>Low-dose inhaled glucocortico-steroid</td><td colspan="2">Low-dose inhaled glucocorticosteroid +LABA</td><td>Medium- or high-dose inhaled glucocortico-steroid+LABA</td><td>Oral glucocortico-steroid</td></tr>
<tr><td>Leukotriene modifier</td><td colspan="2">Medium- or high-dose inhaled glucocorticosteroid</td><td>Leukotriene modifier</td><td>Anti-IgE treatment</td></tr>
<tr><td>-</td><td colspan="2">Low-dose inhaled glucocorticosteroids +leukotriene modifier</td><td>-</td><td>-</td></tr>
<tr><td>-</td><td colspan="2">Low-dose inhaled glucocorticosteroid +sustained-release theophylline</td><td>-</td><td>-</td></tr>
</table>
<u>Management of exacerbations</u>

Repeated administration of rapid-acting inhaled β_2-agonists is the best method of achieving relief for mile to moderate exacerbations.
Systemic glucocorticosteroids should be considered if the patient does not immediately respond to rapid-acting inhaled β_2-agonists or if the episode is severe.

<u>Special Populations</u>

LABAs may also be used to prevent exercise induced bronchospasm and because of a more rapid onset of action, formoterol is more suitable for symptom relief as well as symptom prevention over salmeterol.
Appropriately monitored use of theophylline, inhaled glucocorticosteroids, β_2-agonists, and leukotriene modifiers, specifically montelukast, are not associated with an increased incidence of fetal abnormalities.
Inhaled glucocorticosteroids have been shown to prevent exacerbations of asthma during pregnancy.
Acute exacerbations during pregnancy should be treated with nebulized rapid-acting β_2-agonists and oxygen. Systemic glucocorticosteroids should be instituted when necessary.

</td></tr>
<tr><td>Global Initiative for Chronic Obstructive Lung Disease (GOLD): Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (COPD) (2008)[19]</td><td>
<u>Diagnosis</u>

A clinical diagnosis of COPD should be considered in any patient who has chronic cough, dyspnea, excess sputum production, or history of exposure to risk factors including smoking.
A diagnosis of COPD should be confirmed by spirometry.
COPD patients typically display a decrease in both Forced Expiratory Volume in one second (FEV_1) and FEV_1/ Forced Vital Capacity (FVC) ratio.
The presence of a post-bronchodilator $FEV_1/FVC<0.70$ and $FEV_1<80\%$ predicted confirms the presence of airflow limitation that is not fully reversible.
A detailed medical history should be obtained for all patients suspected of developing COPD.
Severity of COPD is based on the level of symptoms, the severity of the spirometric abnormality, and the presence of complications.
Bronchodilator reversibility testing should be performed to rule out the possibility of asthma.

</td></tr>
</table>

Clinical Guidelines	Recommendations
	• Chest radiograph may be useful to rule out other diagnoses. • Arterial blood gas measurements should be performed in advanced COPD. • Screening for α_1-antitrypsin deficiency should be performed in patients of Caucasian decent who develop COPD at 45 years of age or younger. • Differential diagnoses should rule out asthma, congestive heart failure, bronchiectasis, tuberculosis, diffuse panbronchiolitis, and obliterative bronchiolitis. Treatment • Patients should be instructed to avoid the exacerbating exposure. This includes assisting the patient in smoking cessation attempts and counseling the patient on how to avoid pollutant exposures. • The management of COPD should be individualized to address symptoms and improve the patient's quality of life. • None of the medications for COPD have been shown to modify long-term decline in lung function. Treatment should be focused on reducing symptoms and complications. • Administer bronchodilator medications on an as needed or regular basis to prevent or reduce symptoms and exacerbations. • Principle bronchodilators include β_2-agonists, anticholinergics and theophylline used as monotherapy or in combination. • The use of long-acting bronchodilators is more effective and convenient than short-acting bronchodilators. • For single-dose, as needed use, there is no advantage in using levalbuterol over conventional nebulized bronchodilators. • Inhaled corticosteroids should be used in patients with an FEV_1<50% of the predicted value. • Chronic treatment with systemic corticosteroids should be avoided due to an unfavorable risk-benefit ratio. • COPD patients should receive an annual influenza vaccine. • The pneumococcal polysaccharide vaccine is recommended for COPD patients ≥65 years old or for patients <65 years old with an FEV_1<40% of the predicted value. • Exercise training programs should be implemented for all COPD patients. • Long-term administration of oxygen (>15 hours/day) increases survival in patients with chronic respiratory failure. Management of Exacerbations • The most common causes of an exacerbation are bronchial tree infections and air pollution. • Inhaled β_2-agonists, with or without anticholinergics, and systemic corticosteroids are effective treatments for exacerbations of COPD. • Patients experiencing COPD exacerbations with clinical signs of airway infection may benefit from antibiotic treatment.
National Institute for Clinical Excellence (NICE): **COPD: National Guideline on the Management of COPD in Adults in Primary and**	Diagnosis • Diagnosis should be considered in patients >35 years of age who have a risk factor for the development of COPD. • The primary risk factor is smoking. • Spirometry is diagnostic of airflow obstruction. Airflow obstruction is defined as FEV_1<80% predicted and FEV_1/FVC<70%.

Clinical Guidelines	Recommendations
Secondary Care (2004)[20]	Treatment • Smoking cessation should be encouraged for all patients with COPD. • Short-acting bronchodilators, as necessary, should be the initial empiric treatment for the relief of breathlessness and exercise limitation. • Long-acting bronchodilators (β_2-agonists and/or anticholinergics) should be given to patients who remain symptomatic even with short-acting bronchodilators, if two or more exacerbations occur per year. • Inhaled corticosteroids should be added to patients on long-acting bronchodilators to decrease the frequency of exacerbations in patients with an $FEV_1 \leq 50\%$ of the predicted value. • Oral corticosteroids should be reserved for those patients with advanced COPD. • Theophylline should only be used after a trial of long-acting and short-acting bronchodilators or if the patient is unable to take inhaled therapy. Plasma levels must be measured since there is a larger side effect burden with theophylline. • Pulmonary rehabilitation should be made available to patients. • Noninvasive ventilation should be used for patients with persistent hypercapnic respiratory failure. Management of Exacerbations • Patients with exacerbations should be evaluated for hospital admission. • Patients should receive a chest radiograph, have arterial blood gases monitored, have sputum cultured if it is purulent, and have blood cultures taken if pyrexial. • Oral corticosteroids should be used in all patients admitted to the hospital who do not have contraindications to therapy. The course of therapy should be no longer than 14 days. • Oxygen should be given to maintain oxygen saturation above 90%. • Patients should receive invasive and noninvasive ventilation as necessary. • Respiratory physiotherapy may be used to help remove sputum. • Before discharge, patients should be evaluated by spirometry. • Patients should be properly educated on their inhaler technique and the necessity of usage and should schedule a follow up appointment with a health care professional.

Conclusions

Inhaled corticosteroids (ICS) have evolved into the cornerstone of drug therapy for long-term asthma control. The single entity inhaled corticosteroids are Food and Drug Administration (FDA) approved for the maintenance treatment of asthma as prophylactic therapy. They are also approved for asthmatic patients requiring oral corticosteroid therapy. Current clinical evidence does not demonstrate that one ICS is safer or more efficacious than another.[23-68]

Asthma guidelines stress the role of ICS as long-term controller medications. Both the National, Heart, Lung, Blood Institute (NHLBI) and the Global Initiative for Asthma (GINA) guidelines state that ICS are the preferred treatment for initiating therapy in children and adults of all ages with persistent asthma. It is important to note, that the current consensus guidelines do not give preference to one ICS over another.[17-18]

ICS agents are frequently prescribed in patients with chronic obstructive pulmonary disease (COPD). Both the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, as well as the National Institute for Clinical Excellence (NICE) COPD guidelines recommend ICS as add-on therapy to long-acting bronchodilators in patients with an $FEV_1 \leq 50\%$ predicted and repeated exacerbations.[19-20]

Recommendations

In recognition of the well-established role of the inhaled corticosteroids for the treatment of asthma, as well as chronic obstructive pulmonary disease (COPD), their equivalent efficacy and safety in the management of both disease states, cost considerations and the lack of availability of these agents as generic entities, no changes are recommended to the current approval criteria.

Nonpreferred metered-dose inhalers (Aerobid®, Aerobid M®, Alvesco®) require prior authorization with the following approval criteria:

- The patient has been started and stablized on the medication.

OR

- The patient has had a documented side effect, allergy, or treatment failure to at least two preferred agents.

Budesonide Inh Suspension requires prior authorization, for patients over the age of 12, with the following approval criteria:

- The patient has been started and stabilized on the medication.

OR

- The patient requires a nebulizer formulation.

Pulmicort Respules® requires prior authorization, for patients over the age of 12, with the following approval criteria:

- The patient has been started and stabilized on the medication.

OR

- The patient requires a nebulizer formulation.

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